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ADDRESS OF THE PRESIDENT*

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THERE is no accounting for the twists of fate that affect our lives. Here I find myself the President of this distinguished Society, yet I still cannot figure out why you should have been so unaccountably partial in your choice. My incoherent remarks of acceptance at last year's meeting were about as inadequate in expressing my appreciation as they are now in thanking you for having accorded to me the privilege of letting me share in the guidance of this distinguished Society. I hope you will believe that my thanks, though still inadequate, nevertheless are most sincere.

Since it is the traditional obligation of the President to deliver an address, I bow to the inevitable, though I should prefer to remain silent, for, as the Japanese saying goes, the silent man is best to listen to. My predecessor brought you up to date on the state of the Society in his erudite address and there is little to add for the past year that warrants inclusion here except to record the election of three Fellows to active membership: A. N. Arneson, John Parks, and Herbert E. Schmitz, and the passing of seven of our Fellows who have left an indelible impression on the pages of our annals. I report with deep regret the death of Thomas Watts Eden, Klaas DeSnoo, and George L. Streeter, Honorary Fellows; Jennings C. Litzenberg, Franklin S. Newell, and Howard C. Taylor, Life Fellows, and Henricus J. Stander, an active Fellow.

I have not found it simple to select a subject of general interest which has not been discussed wholly or in part by other Presidents of this Society. After

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much vacillation I finally decided on a topic which seemed timely and of common interest and with which I have a better than speaking acquaintance. I shall inflict upon you some of my views on the trends in cancer research and on certain teaching problems concerned with cancer. Do not expect to hear an erudite recitation of the many facets of investigation nor a learned review of the efforts of the many who have searched for an answer to a timeless enigma. My remarks simply are reflections that I like to air and I could not think of a better opportunity than to do this among men whom I consider broadminded and thoroughly conversant with the subject matter of this address.

I believe it not presumptuous to state that there is a need for a dispassionate re-evaluation of our thinking on the broader aspects of cancer research because there is ample evidence that it is drifting into a world of its own, steadily expanding in scope, but equally fast moving away from the human problem. The late James Ewing said some ten years ago that "the ramifications of the interest in cancer, which reach into many branches of human knowledge, form a broad basis which assures sound progress, but at the same time become a definite menace, because when every type of investigation claims a relation to cancer, the resources become dissipated over too vast a territory and are apt to lose practical value." This conclusion still holds.

As one reads the important reviews of cancer research, one cannot escape the feeling that there is serious doubt in the minds of many regarding the ultimate value of the present trends in cancer research and that a new approach, more closely related to the human problem, must be found. I do not mean to be critical but it seems to me that research not only must make an inventory of its achievements on the basis of an objective evaluation, but that also we should inquire critically whether the public interest in cancer research is intelligent or largely emotional and uncritical, just as we should inquire quite as critically whether the resources that are now being poured into this field are wisely invested or largely wasted in terms of service to humanity.

There is good reason to believe that a considerable portion of cancer research is not efficiently planned and is largely of the variety that Lord Chesterton described as the effort of the blind man looking into a dark closet for a black hat that is not there. The usual defense for this type of research is that it deals with pure science and that as such it adds to the sum total of basic knowledge. Some, no doubt, is, but much more is not, but constitutes solely an irrelevant variety of sporadic exploits largely based on that forlorn hope that some great discovery may result from it purely by accident. Yet, time and experience have proved conclusively that only skillful planning based on broad scientific experience and endless perseverance can produce the really worth-while contributions to the knowledge of cancer. Most of the work of the other variety has gone by the board and has served no other purpose than to clutter up the literature. At best, cancer research of the serious variety is painfully slow in yielding important results because even under the

most propitious conditions there are limits to all efforts, which are beyond our control, because the system with which we work is inconstant and subject to a limitless variety and variability of the aggregates to be studied and to be correlated. Irrelevant research, therefore, should be discouraged for there is no reason to believe that the present state of the knowledge of cancer justifies the hope that a sensational solution is just around the corner. No doubt we need sound fundamental research to understand basic phenomena, but I believe, too, that the time has come to ask those engaged in the study of the pure sciences to lend a more helpful hand with the human problem because our efforts to stem the tide of malignant disease rapidly are approaching an impasse.

To illustrate my contention that cancer research must take a different attitude toward the human problem, I shall cite briefly what has happened to the study of irritation in relation to cancer. The idea that irritation might cause cancer is very ancient and antedates Hippocratic teachings. However, the basic theory of irritation as we know it stems from Galen who formulated it on the basis of his own observations and deductions. Quite naturally twenty centuries have modified the modus operandi of his thinking, yet a vast amount of experimental inquiry has not brought us materially closer to the solution of the human problem. This is forcefully brought out when one evaluates critically the meaning of the carcinogens. We now know many of such substances and we are familiar with their behavior in animal experimentation. Yet, the vast effort necessary to produce this knowledge has failed to give us even as little as a hint how to solve our clinical problem for we still do not know, for instance, why aniline dyes create cancer of the bladder in man. Fundamental research has been content with producing cancer of all sorts in small laboratory animals with a variety of unrelated chemical compounds, yet it has made little or no effort to determine the nature of the specific irritant that produces bladder cancer in aniline dye workers. That is what I mean by saying that fundamental research is drifting into a world of its own and away from the human problem. If all of the hundreds of carcinogens now listed actually were factors in the production of human cancer, I fear that by now most of us should have succumbed to the disease.

We have a similar problem confronting us now in our own specialty. I have reference to the possible relation of the estrogens to cancer. This subject certainly is in a highly controversial state. A vast amount of fundamental research has been done, largely on small laboratory animals, yet it has served to obscure rather than to clarify the problem, and it also has done much to add further fuel to the already upset emotions of the public in their thinking on cancer. The immense amount of human cancer material flowing through the clinics of the world hardly has been tapped for extensive hormone studies. The few limited studies undertaken are at variance with most of the conclusions derived from the study of small laboratory animals. Yet, estrogens have been injected, implanted, and fed to human beings for nearly thirty years. Should we not encounter by now some increase in certain forms of cancer

in our treatment centers if these hormones necessarily were primary factors in carcinogenesis, as we have been told many times by some of those whose whole concern is the laboratory animal? Or, could it be that in terms of human life the time of observation elapsed is too short as interpreted in terms of small animal experimentation? Here is another gap between pure laboratory research and clinical experience that must be bridged by the trained research worker in conjunction with the clinician, and it can only be bridged through an approach of the human problem. It may prove eminently more complicated and cumbersome to carry out this task, but it should prove definitely more useful to the human race than the relatively uncomplicated and very comfortable approach through the laboratory animal. The richest fuel for creative power comes from firsthand information. Somebody, I do not recall who, once said that we surely will gain more from milking a cow than from looking at the milk bottles on the window sill, and that goes for a lot of present-day cancer research. To be sure, I am not deprecating fundamental research for I fully appreciate the heroic efforts of the really serious, well-trained, and experienced investigators who forsoook the fleshpots for the sake of science, and besides, I speak from within the ranks, having spent a large part of my life in the sanctity of the laboratory. But the more I see and hear of present trends in cancer research, the more I become convinced that the ivory-tower attitude many research workers assume should be abandoned in favor of a resurgence toward the study of man. There can be no doubt that we need the help of the trained research workers in solving our cancer problems, but we need a much closer cooperation between the laboratory and the clinical fields than has been achieved up to now. Where such cooperation exists, it has yielded rich returns. I only need to point at the development of the cytologic screening methods which resulted from the mutual efforts of an anatomist and a gynecologist.

I must not prolong this discussion by a recital of the various cancer problems that confront us for they are thoroughly familiar to you. My aim in bringing my thoughts to you on the present trends in cancer research is to provoke a discussion in the hope of stimulating a closer approach between research and clinical practice. Anybody interested in the study of cancer must realize that we are faced constantly with the workings of two lines of thought. One is based on the struggle of experience against theories and the other is the use of the experimental method in determining the true significance of experience. There is as great a need for theoretical research now as there always has been, but some attempt must be made to strike a balance once in a while or clinical knowledge and fundamental research ultimately will become unrelated. Lancelot White, the Scottish physicist, once said that "the scientist must go out in search of facts, but he must also sometimes pause to arrange them." And, elsewhere, he added that every great movement is in essence simple and that resistance serves to challenge the new to greater efforts of discipline and achievement. To which I add that we do not live just to have experience but to learn from it. Living in a world of living men, we must have

a horizontal view of life; living at a point on a long road of research we want a vertical view of results. The individual concerned with the study of cancer must take his place where the horizontal and vertical views cross, somewhat like locating a target through a bomb sight.

Another problem of considerable interest to me concerns itself with the teaching of cancer to medical students as well as to graduates. I feel sure that all of you are aware that considerable discussion is now under way within and between teaching institutions for the purpose of reviewing methods used in the teaching of cancer. The suggestion has been made that all teaching of cancer might best be handled by those who devote their entire time to the study and treatment of malignant diseases. In fact, in some thirteen medical schools departments of oncology have been organized. This tendency to segregate cancer from the body of medical teaching is looked upon with favor in various quarters actively engaged in the collection and distribution of funds to be used in the fight against cancer. The U. S. Public Health Service, acting as the guardian of Federal money set aside by Congress for such purpose, has requested that grants to medical schools should be the concern of a "cancer coordinator," which I picture as something of a cross between a major-domo of the faculty possessed of an encyclopedic knowledge and a sort of commissar empowered to direct our thinking on the subject of cancer. There actually exists now an organization of such cancer coordinators who meet to exchange ideas and formulate policies to be submitted to their respective faculties. The upshot of a recent meeting was that while medical schools have different teaching programs the common emphasis is about the same in all programs. To arrive at this momentous conclusion valuable time and government money were spent to no purpose except to discover what long since has been common knowledge among medical teachers.

In conjunction with the proposal to institute cancer coordinators there also has been some talk about the advantages of "vertical" versus "horizontal" teaching; the former to mean that all teaching of cancer is to be delegated to a coordinator or a so-called cancer expert who will treat the subject as a distinct specialty; the latter to mean that all teaching of cancer shall remain as heretofore part and parcel of the broad teaching of medicine and surgery, or in other words, that cancer shall be taught as it concerns the patient and not just as it pertains to the organ. It is my understanding that under the "vertical" scheme of teaching an otherwise competent and experienced clinician may tell all there is to know about his particular field except cancer. When that subject comes up for discussion he must yield to the cancer expert who then teaches that subject as something entirely apart. I do not know from what quarter such thinking has emanated, nor is that a matter of importance, for the fallacy of "vertical" teaching will be recognized by all experienced medical teachers as curricular gadgetry. Advances in the knowledge of the nature of cancer and its treatment are coming along at snail's pace; I cannot conceive of a seasoned and accomplished medical teacher incapable of keeping abreast with factual cancer knowledge such as is usable

for student teaching. The vast mass of cancer research, with a few outstanding exceptions, is not immediately usable for such teaching since such knowledge is notably irrelevant in its relation to clinical practice. It would be disastrous to burden the student with the many fanciful flights into abstract research when already he is so very close to his capacity of coping with a huge and often indigestible amount of reading. The U. S. Public Health Service which also is interested in placing funds for the improvement of teaching facilities wisely has refrained up to now from issuing an official blueprint for planning a cancer teaching program but has assumed the attitude that for the present each school must work out its own program in whatever manner it might fit local needs and facilities. And that is as it should be under the rules of academic freedom in any true democracy. This rather unusual attitude on the part of a Federal agency entrusted with the dispersal of public moneys is refreshing and most commendable, and I like to believe that this attitude is as sincere as it is far-sighted. I do not like to think that any agency holding the strings to a well-lined purse is desirous of injecting itself into our planning and thinking because we are desperately in need of additional funds to enlarge existing diagnostic and therapeutic facilities, but at times I sense such an attitude though I fervently hope that I am mistaken. The tendency to overorganize medical teaching is a curse in itself and should be resisted before it brings other evils detrimental to academic freedom. To submit to the dictates of an outside agency just for the sake of much needed financial support beyond the accountability for moneys received would be intolerable and certainly destructive to the thinking of free men and women. I leave it to you to judge for yourself what stand to take in this controversy.

It is rather interesting to learn what outsiders think of our ways of teaching medicine. Recently, I read in *Cancer News* (January, 1949) a reference to certain schemes of teaching. It was pointed out that because various segments of information are not integrated, the medical student graduates without obtaining the necessary composite picture of cancer and with only a fragmentary knowledge of the basic diagnostic methods and recommended forms of treatment. Because this journal is widely read such a statement should not remain unchallenged since it implies indifference on the part of the teaching profession toward a very pressing problem. If this statement were based on irrefutable evidence I should be the first to acknowledge its merit and promptly take a hand in initiating a move to correct the evil. Although I can speak only for our far-Western medical schools whose quality of teaching I am thoroughly familiar with, I would like to go on record that the statement cited is not based on fact and exhibits a lack of insight into the teaching problems and curricula offered by all progressive medical schools. There is no denying that there always is room for improvement, but what serious teacher would ever stop at making improvements according to circumstances and whenever new discoveries warranted their acceptance? Quite naturally, teaching methods vary to some extent in different institutions and the views of teachers vary according to personal experience, but in principle the philosophy behind

the teaching differs but little since its common aim is to make the student conscious of disease in all its form as well as proficient in the fundamentals of diagnosis and treatment. This very same principle applies to the teaching of cancer. What the public fails to understand is that in the short span of four years we cannot turn out a finished technical expert experienced not only in the treatment of all diseases but also possessed of the judgment of a sage. Evidently, our critics fail to understand that there is not only a limit to the volume of teachable material but also a limit to the individual capacity of the average student to absorb and digest what is being taught and that even carefully selected students are subject to mental fatigue in spite of youth and physical stamina. Yet, it is exactly that individual capacity to learn and to retain which, in the end, largely determines the ultimate performance of a physician. Even under the best of teaching conditions the most that can be hoped for is that every student at the end of the prescribed years of learning has been grounded sufficiently in the fundamentals on which to build the edifice of his future performance in medical practice. We cannot produce experts in any branch of medical practice in four short years and the public should be told about this often enough to realize the limitations of the best of teaching schemes.

There is another important factor in teaching which the public does not understand and that is that the ultimate result of modern teaching in medicine is not dependent upon bigger and better buildings but upon the limitations in the number of students to be taught in conformity with the clinical material necessary for good teaching and the size and quality of the faculty available to convey information to the student in such a manner that what is taught will make a lasting impression. Yet there is constant pressure being brought upon medical schools to enlarge the size of their classes without due regard to the factors cited. Good teachers in medicine are becoming scarce because like all other teachers they are underpaid on the whole. Yet, it is only a good teacher who can establish a satisfactory student-teacher relationship which is the acme of sound teaching. Large classes are detrimental to a close relationship between teacher and student. The average layman takes it for granted that any doctor of medicine can be a teacher and hence there should be no shortage, and I dare say that many doctors of medicine labor under the same delusion. But I know from long experience that this is just wishful thinking on the part of those who would like to sun themselves in the reflected glory of a teaching institution. Teachers are born, yet they still must learn the mechanics and philosophy of teaching before their teaching achieves the soundness that removes it from the level of textbook recitation. The old style lecture is a matter of the past. Its place has been taken by teaching methods which more closely approach the spirit of the Socratean dialogue. This in turn calls for teachers possessed of more than book learning and at the same time capable of imparting the meaning of knowledge to students. Effective teaching in that sense limits the number of students to be taught. Any deviation from this principle invites the workings of the "law of dimin-

ishing returns'' with the inevitable consequence of reducing the quality of teaching. I call on all those who take great pride in modern methods of medical teaching to resist the attempts of outside agencies to tempt medical faculties with financial baits in exchange for an increase in the present size of classes, unless certain prerequisites have been satisfied. With the limitation of clinical material and the scarcity of trained teachers, money alone and increased physical facilities evidently are not the answer. Before agreeing to an increase in the enrollment to our medical schools, we first must improve the material status of the medical teachers in order to attract enough of the right individuals trained and experienced in proper teaching methods. Then we must increase our clinical material sufficiently through free care and free hospitalization which many institutions are unable to afford for obvious reasons. Only then should we give thought to an increase in our enrollments. Since it is all a matter of finances a good share of the available moneys now diverted to irrelevant cancer research could be employed to better advantage if used for clinical purposes. If there were a place for a cancer coordinator it should be there.

We are living in a very critical period so far as the future of medical teaching is concerned. I am sure that you, too, have been wondering what would happen to medical teaching should medicine become socialized with a free choice of doctors. I am convinced that it would reduce our clinic material to a negligible quantity, for the average American citizen most certainly would abandon the teaching clinic in favor of private care. The public, no doubt, will think this a good argument for socialized medicine, and in the light of American thinking of equality and human rights it is, yet, in the light of medical teaching it would result in a return to archaic methods of instruction which would set us back fifty years. It would call for a complete reorganization of medical teaching probably controlled by government decree.

So far as the present status of the teaching of cancer to medical students is concerned, I am content that it is in line with all other medical teaching and that it is well integrated with the sum total of teaching matter. I sincerely believe that it is practical within the limitations already discussed and that it is sanely presented within the scope of undergraduate instruction. Therefore, I urge that the teaching of cancer be not dissociated from the general body of medical instruction by fanciful schemes emanating from pressure groups but that it be left in its logical position in the time-tried method of horizontal teaching.

Postgraduate teaching of cancer is undertaken primarily for the benefit of the busy general practitioner who represents the first and most important line of defense against all diseases. It has been stressed that because of the time lost between the recognition of cancer and the institution of efficient treatment the cure rate cannot improve materially until this time interval has been reduced drastically. Postgraduate teaching hopes to eliminate this factor with the aid of various agencies and state and county medical societies through various approaches to the problem.

Postgraduate instruction in cancer is relatively uncomplicated as it relates to residency training in approved hospitals where adequate time and material and experienced supervision give the graduate every opportunity to reach a high degree of proficiency in technical matters and where the long association with earnest and scholarly staff members implants and germinates the seeds of thirst for knowledge.

The situation, however, is vastly different for that large group of medical graduates who by dint of circumstances must enter into the practice of medicine after relatively short periods of hospital training. Yet, this group constitutes by far the greater mass of practitioners on whom the public depends for the safeguarding of life and health. The breadth of general practice puts not only an immense physical burden upon the shoulders of these courageous men and women, but it also demands a range of knowledge often beyond individual capacity since even general practitioners are only human and often very tired humans. The often cited excuse that because many general practitioners, at best, see only an occasional case of cancer in many months and that, therefore, it should not be expected of them to be adequately experienced in the intricacies of the disease, of course, is no more tenable than failing to suspect the presence of any rare disease. It is a matter of mental disipline to keep alert rather than a matter of technical experience alone. If the humdrum of daily routine and the material success of practice have not entirely destroyed the intellectual capacity of a practitioner, he certainly must have preserved enough of the fundamentals of his teaching and training to be able to measure his own knowledge, and if found not to be adequate, to venture forth in search of additional information. Are we as teachers responsible to keep forever on the trail of our graduates in order to keep them up to the level of expected performance, or is the individual responsible to achieve such ends by his own efforts? I believe that the latter is the real crux of the whole problem. Other professions do not tag after their members in order to spoonfeed them, yet we do because we are keenly aware of our responsibility to humanity. For some time I have been wondering if we are achieving actually what we hope to achieve by our present methods of postgraduate teaching.

As you well know small bands of zealous practitioners, many of them professional medical teachers, have traveled about the land far and wide to enlighten the busy doctor on the subject of cancer. Conferences, refresher courses, formal postgraduate sessions solely devoted to cancer are held in many centers at frequent intervals. By and large, this form of postgraduate teaching is sound in spite of its limitations. I have participated in and followed this trend of delivering knowledge in small packages for some years, but I also have become convinced gradually that the dispensing of technical knowledge alone is not enough to achieve our ends. Do the participants actually return to their own spheres of activity mentally prepared to feed the fire kindled by the spark of a graduate session? Has it really awakened a new interest in the potential dangers of delayed diagnosis? Is it just enough for us to present over and over again the details of diagnosis and treatment

that can be read just as readily at home, provided the art of reading has not been lost? I am certain that it is not. Theologians have pointed out since time immemorial that professing to a creed and living one's religion are two very different moral entities of which only the latter is of true importance. In medicine we deal with exactly the same balance of values. There is a wide difference between practicing the art of healing and living the practice of medicine. One is the means to an end but the other is the living up to an ideal which is more important whatever way one looks at it. I sincerely believe that while there is constant need for technical improvement there is even greater need for a re-evaluation of individual integrity and the implied obligations concomitant with the practice of medicine. Unless we teach the broader philosophic ideals of practice in conjunction with the technical details, I fear that postgraduate sessions on the whole have missed a golden opportunity. I believe that there is great need for emphasizing that whoever takes up the burden of safeguarding life, limb, and human happiness must do so solely in the best interest of the patient. If we earnestly strive to put over this message, I am at least hopeful that it will aid in improving the thinking on cancer. If, on the other hand, we are content with barnstorming merely to stuff the practitioner with a multitude of technical facts and statistics and dazzle him with visual demonstrations, which often leave him bewildered, we have not conveyed to him the true message of improving the diagnosis and treatment of cancer.

I should have liked to touch on several other phases of the cancer problem, such as the education of the public and the meaning of statistics, but I must not exhaust your patience. I regret that there can be no discussion from which I could profit. However, the writing of this address has helped me immeasurably to clarify my own thinking. In presenting it to you I have been guided by Paul's advice to the Corinthians: "Unless ye utter by the tongue speech easy to be understood, how shall it be known what is spoken? For you shall have spoken into the air."

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THE VALUE OF THE VAGINAL SMEAR*

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THE Vincent Memorial Laboratory has used the vaginal smear as an aid in the diagnosis of uterine malignancy since 1942. This report is our experience with the method in this six-year period and a discussion of its application in carcinoma of the cervix.

The cytologic diagnosis of cancer is based upon the fact that both normal and cancer tissue shed cells continuously from their surface. There is evidence that the desquamation from malignant tissue takes place more rapidly than from normal tissue. Coman in 1944[1] in a unique way measured the force required to pull cells apart. The force required to separate normal cervical cells was ten times that required to separate the cells of squamous carcinoma of the cervix. This characteristic of cancer tissue facilitates the diagnosis of cancer by identification of exfoliated malignant cells. Though the normal cells are almost always in the majority, numbers of cancer cells usually desquamate, even in early lesions.

The method by which these desquamated cells are obtained, placed on a slide, and fixed, varies from laboratory to laboratory. Vaginal, cervical, endocervical, or endometrial smears may be done. Scraping of the cervix with a wooden spatula and then placing those cells on a slide has been advocated by Ayre.[2] Fixing a large mass of vaginal secretion and running the mass through the usual histologic technique for pathologic tissue had been advocated by Hunter.[3] Our experience has dealt almost entirely with the vaginal smear. We have used it almost exclusively since we felt that one of the great advantages of the method was the simplicity of obtaining material. To add additional equipment and complicate the process seemed to lessen this advantage. We have used the curved glass pipette and bulb to aspirate the secretions collected at the posterior fornix. In special cases all types of smears are done, but for routine purposes we have relied on the vaginal smear. All smears have been stained by the method of Papanicolaou.[4]

In a six-year period we have studied 8,133 cases by means of the vaginal smear. The statistics presented here are based on the *initial* smear. If, in a case of carcinoma, the first smear was negative and the second one positive, the case is catalogued as an error in diagnosis. If the statistics were based on individual smears, the accuracy would be much higher. In this period of time there have been 432 carcinomas of the cervix, 401 of these squamous and 31 adenocarcinoma. Ninety per cent have been diagnosed correctly by cytologic examination. Thus, the false negative figure in this group of cases is 10 per cent. Let us examine our results as to the accuracy of diagnosis in early carcinoma. In 40 cases of carcinoma in situ of the cervix, the initial vaginal smear

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was positive in 35, or a percentage error of 12.5 per cent. In the same group of cases, the biopsy failed to discover the preinvasive lesions in 12, or 30.0 per cent. Thus, in our experience, the routine vaginal smear is more accurate than routine biopsy in the diagnosis of preinvasive carcinoma of the cervix. The major reason for the failure of biopsy to reveal a higher percentage of accurate diagnoses in carcinomas is that, if the carcinoma is small and the cervix presents no abnormalities grossly, it is extremely difficult to choose accurately the site of biopsy. Obviously, if multiple biopsies are taken, the diagnostic accuracy of the biopsy method will be increased. However, with single routine biopsies, the accuracy of diagnosis has not been as high as that of single routine vaginal smears in early carcinoma of the cervix. A real advantage of the cytologic technique is that the diagnostic accuracy is greater in the early carcinomas than in those which are far advanced. The cytologic method depends on the desquamation of well-preserved cancer cells. If the tumor is far advanced, the surface may be necrotic and no cancer cells will be picked up on the smear. On the other hand, early tumors have a well-nourished surface, and the cancer cells which desquamate are in considerable numbers and are readily identified. An additional advantage is that the vaginal secretions contain representative cells from all surfaces of the genital tract so that the region examined is not limited by the size or location of the sample taken.

There has been much discussion of the possible use of the vaginal smear in a widespread screening of well women. We have not had any experience with wide-scale use of the method in this way, but gradually more routine smears have been sent to the laboratory. We have been impressed with the number of early and often symptomless carcinomas discovered in even small-scale screening. In 305 cases screened in the office of one of our medical colleagues,[5] five carcinomas were discovered, four of them cervical. Three of these cases had no bleeding or discharge, and the cervix appeared normal to inspection. Case report:

M. G., aged 43 years.
Chief complaints: Diarrhea and arthritis. No bleeding or discharge.
Local examination: Cervix appeared lacerated.
Vaginal smear: Positive and consistent with squamous carcinoma.
Biopsy: Carcinoma in situ.
Operation: Radical hysterectomy with bilateral dissection of pelvic lymph nodes.
Pathologic report: Gross examination: Cervix appeared normal to inspection
Microscopic examination: Squamous cell carcinoma in situ.

In a moderate screening test on all patients entering the Gynecologic Out Patient Department of the Massachusetts General Hospital, five early carcinomas of the cervix were found in 735 patients.

These figures are higher than those expected in screening all women. Lombard,[6] from the Massachusetts State Cancer Commission, reported an incidence of 0.2 per cent. Our figures of 0.7 per cent in contrast to the above, may suggest that, from a practical point of view, perhaps a higher percentage of unsuspected cases may be found in screening office patients or part of a hospital population than in wide-scale screening of well women.

We have found the vaginal smear of use in the routine follow-up of patients treated for malignant disease. In three instances, postradiation recurrences were detected though the patients appeared free of disease clinically. In each instance positive biopsies were only obtained when the adhesions at the vaginal apex were broken, the disease in all instances being behind the adhesions. One early postoperative recurrence was discovered by cytologic

examination. In an evaluation of the status of the treated cancer patient, we feel the vaginal smear is an essential part, and do vaginal smears routinely on all patients entering the Gynecologic Tumor Clinic.

Of the 432 cases of cervical carcinoma diagnosed by vaginal smear, 38 or 8.7 per cent are considered to be unsuspected. Of these, 19 had no discharge or bleeding, and their cervices appeared normal to inspection. The only reason for obtaining a biopsy in these patients was the positive cytologic finding. The remaining 19 had some symptoms which might have pointed toward malignancy, but the symptoms were minimal and rationally explained on some other basis, such as withdrawal bleeding after estrin therapy. We believe that, in these instances, the carcinoma would have been discovered much later if the cytologic examination of the vaginal secretion had not been used. Of the 38 cases which are considered unsuspected, 28 were carcinoma in situ, and 10 were invasive carcinoma. In our hands the cytologic examination of vaginal secretion has proved of value in the detection of early carcinoma in a limited screening of symptomless women and in the follow-up of treated malignancy.

What of the other side of the picture? How specific is the test? Are false positive diagnoses numerous? During the first year in which we interpreted vaginal smears, the false positive figure was 6.4 per cent. As shown in Table I, the error has been reduced until during the year of 1948, of 2,420 negative cases, only one case was called positive erroneously. This is a 0.04 per cent false positive error. The steady reduction in error can only be attributed to increased experience in differentiating atypical benign cells from carcinoma cells. In the past two years, we have not had a case in which the vaginal smear was positive and consistent with squamous carcinoma that has not been proved histologically to have been squamous carcinoma. The single false positive made in 1948 was thought to present the cytologic picture of an adenocarcinoma of the endometrium. With experience in the microscopic interpretation, the specificity of a positive diagnosis of squamous carcinoma is so high that a presumptive diagnosis of carcinoma must be made.

TABLE I

YEAR	NEGATIVE CASES	FALSE POSITIVES	PER CENT ERROR
1943	265	17	6.4
1944	875	15	1.7
1945	962	14	1.4
1946	1,292	18	1.4
1947	1,897	5	0.2
1948	2,420	1	0.04

The practical or economic aspects of the method must be considered. How much does it cost and how much time does it take? (The cost per slide to the patient is two to five dollars.) The major portion of the expense is salaries of technicians and this will vary with the amounts paid in salaries. The equipment needed for the method is limited and is not expensive. A figure between two and three dollars' cost per slide should be regarded as an estimate. The time required to study each slide is much more difficult to answer. Obviously, some smears may be called either negative or positive with assurance in a very few

minutes; others take considerable time. On the average, a well-trained technician can screen a slide adequately in ten minutes, yet this is only an estimate. The cost or time required per slide is not prohibitive and neither should prevent widespread application of the method. The most serious bottleneck is the lack of well-trained personnel.

We should like to emphasize that the vaginal smear is not a substitute for biopsy as a method of diagnosis of cervical carcinoma but is a complementary method. In 1948 one of us did a comparative study between the initial diagnosis by vaginal smear and by biopsy in 181 primary carcinomas of the cervix.[7] The vaginal smear was negative in 17, or 9.4 per cent; the biopsy in 19, or 10.5 per cent. Thus there was no significant difference. However, if both methods were used together, the diagnostic accuracy was 98.3 per cent since only three cases were missed by both methods. This indicates that neither method should be used to the exclusion of the other, and that if both methods are used together, the accuracy of diagnosis will be higher than if either one is used alone.

TABLE II PRIMARY SQUAMOUS CARCINOMA OF THE CERVIX (181 CASES)

INITIAL CYTOLOGIC REPORT	INITIAL BIOPSY REPORT	NO.	PER CENT
+	+	148	81.7
+	–	16	8.8
–	+	14	7.7
–	–	3	1.7
		181	99.9

Finally, a word should be said about the interpretation of reports of cytologic examination. Since there are 10 per cent of false negative reports in the cytologic diagnosis of cancer of the cervix, a negative vaginal smear does not rule out the presence of a carcinoma. If signs or symptoms suggest cancer, a negative cytologic report should not be considered seriously. A positive vaginal smear, however, is of extreme importance, and the physician is obligated to make an extensive search for the carcinoma. We do not advocate radical surgery or radiation treatment on the basis of a positive cytologic report, but believe that the positive vaginal smear should be confirmed by biopsy. In some instances this will require more than one biopsy, and a real effort must be made to confirm the cytologic finding. If the vaginal smear is used in this way, unsuspected early carcinomas of the cervix will be discovered.

With the curability of carcinoma of the cervix at its present low figure, we cannot afford to disregard any method which offers an additional opportunity to diagnose early carcinoma. The cytologic examination of the vaginal secretion deserves a place in every gynecologic clinic.

Conclusions

1. Cytologic examination of smears in the Vincent Memorial Laboratory since 1942 has proved of great value.

2. There have been 8,131 slides and 432 cancers.

3. The false positive error has diminished until in the last year it was only 0.04 per cent. In other words, a positive smear means the presence of cancer.

4. False negative smears continue at about 10 per cent. This figure is due to lack of cells in advanced cases and a lack of exfoliation in others.

5. Smear and biopsy diagnosis are not rival methods but complementary ones.

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Discussion

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—I welcome the opportunity of opening the discussion of Dr. Meigs' presentation, in which he has been so ably assisted by Mrs. Graham. I know that all of us respect and admire the correctness of his observations and the enthusiasm with which he and his group have always pursued their objectives.

We, in Philadelphia, have had an exceptional opportunity, I feel, to evaluate cytologic methods in the diagnosis of uterine cancer, not only in our own institution but in the city at large, because of the cytologic work that we have done for the numerous Health Maintenance-Cancer Detection Clinics supported by the Donner Foundation in cooperation with the Philadelphia County Medical Society. The Division of Cytology of the Department of Obstetrics and Gynecology at Jefferson Medical College and Hospital is under the direction of Dr. A. E. Rakoff, Assistant Professor in the department and Director of the Endocrine Laboratory of the Institution. His accomplishments are well known to most of you. Miss Dorothy Meyers, our associate and head technician, is an invaluable co-worker. What I am able to present is in a large part due to the conscientious labor of these colleagues.

If a single site is to be used to obtain vaginal smears, then the posterior fornix of the vagina is the best source. However, we prefer to collect smears also from the endocervix, the squamocolumnar junction, and directly from any demonstrable lesion, using both pipette and wooden scraper. We have noted instances in which cervical smears were positive when the vaginal smears were negative.

By taking multiple smears and by obtaining such factual data as age, character of menstrual cycle, any recent hormonal therapy, and clinical features noted, we were able to increase the percentage of "correct positives" from 70 to 82.4 per cent in two comparative group studies of 500 patients each, even though the percentage of "false positives" rose from 1.6 per cent to 2.6 per cent as compared with the essayist's Table II. "False negatives" dropped from 30 to 17.6 per cent.

Between 1943 and 1949 we have studied smears from approximately 14,000 patients, of whom about 8,000 were patients in the wards, outpatient clinics, and private rooms

of the hospital. The remaining 6,000 patients were seen in the various Health Maintenance-Cancer Detection Clinics sponsored by the Donner Foundation of Philadelphia. Our total number of "correct positives" and "correct negatives" in this very large group have not been accurately tabulated because of incompleteness of the follow-up to date. "False negatives," however, average 10 to 15 per cent. "False positives" are less than 1 per cent if we include the Health Maintenance-Cancer Detection Clinics, but 1.5 to 2 per cent on selected patients, due probably to the high percentage of benign lesions seen.

It is true, as the author states, that the smear tends to be more valuable in early than in advanced lesions; hence the method, as the author states, is a valuable adjunct to biopsy. However, it should be emphasized that because of a reported incidence of "false positives" that may run as high as 2 per cent in the hands of even the most experienced observers, the necessity of obtaining a positive biopsy is obvious and essential before actual treatment for cancer is warranted on the basis of a positive smear. In other words, a positive smear and a negative biopsy should not be considered as presumptive evidence of cancer, even in situ. Neither can we dissociate cervical biopsy from endometrial curettage as a practical consideration in the early diagnosis of uterine cancer, whatever its suspected source, and certainly not when we are attempting to "prove" a positive smear to be correct. We have found the circular biopsy more effective than multiple ones.

In a screening study of 5,622 new patients, of whom 3,499 were subsequently examined periodically, a total of 9,121 cytology examinations were made. The results were: 3 positive, 21 suspicious, 50 doubtful, and 9,047 negative. Of the three positives, one patient had the cervix amputated and radium applied seven months previously for carcinoma; in the second, biopsy three months later revealed cervical cancer, and in the third, hysterectomy a month later revealed cervical leucoplakia.

Seven patients had known uterine cancer. Although the smear was positive in six of the seven cases of cancer thus far discovered, six of these patients presented a history together with findings on examination that indicated the need for biopsy and curettage. There was one striking case in which the smears were positive, although the initial examination and subsequent single biopsy were negative. However, subsequent multiple biopsies did reveal cancer. We have also had six patients in whom the smear attracted attention to an unsuspected cancer.

The value of the cytology smear as a screening procedure for "selected cases" will usually be in inverse proportion to a meticulous pelvic examination for which there can never be a real substitute. The experienced clinician uncovers salient points in the history or detects lesions on thorough examination that immediately demand biopsy and/or curettage which a less experienced person may miss or ignore by simply taking a smear. Since the latter may result in a "false negative" in 10 to 30 per cent of cases—and this is the crux of the situation—it is obviously dangerous to give advice or depend upon smears primarily before deciding whether or not a biopsy and/or curettage are indicated. In this sense the smear becomes even more important in those patients whose pelvic examination appears to be grossly normal. The harmful effect of published propaganda on the ease with which smear examinations can detect or rule out cancer, and the mischief causing unwarranted fear on the one hand and a false sense of security on the other have frequently been commented upon by us and by others, and rightly so.

General experience seems to show that as personnel becomes better trained and more experienced, the percentage of "false positives" diminishes. This is especially true when the influence of pelvic inflammatory disease or complications of pregnancy are not apparent, for these are two instances in which difficulty in evaluating smears obtains. On the other hand, as our criteria for positives become more exacting, the tendency to miss more cases may increase. For this reason many cytologists purposely include such categories as "suspicious" or "doubtful" or accept Dr. Papanicolaou's gradation of one to five.

Although in the essayist's hands at the present time a positive smear means to him the presence of cancer, as evidenced by their present figure of ½ of 1 per cent of "false positives," this was not always so and certainly it is not so in the hands of other workers of experience. Hence, the conclusion that "a positive smear means the presence of cancer" is a dangerous one for the profession at large to rely upon.

Finally, the authors come to the same conclusion that we have constantly been advocating: that the vaginal smear is not a substitute for biopsy as a diagnostic procedure, but rather that it is a complementary method.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—I have always believed that, if a proper history is taken and a bimanual and speculum examination made by a competent gynecologist, that he could then assure the patient as to whether or not she had carcinoma or that further procedures were required. Dr. Meigs is a competent gynecologist and he states that he detects an additional 1 per cent of cervical and corpus cancers by the Papanicolaou smear in patients who present no other evidence. In view of his findings, as well as those of other competent gynecologists, I believe some form of screening for uterine cancer is indicated.

I wish to call the attention of the Society to a chemical test for excluding 80 per cent of the patients as not having carcinoma of the cervix. Any technician with some chemical training can learn how to perform the test within a day. Dr. Lester Odell on our service has found that if the beta-glucuronidase value of the vaginal fluid is less than 300 μg, he can exclude all of the cases as not having carcinoma of the cervix and possibly the same for the corpus. Eighteen per cent of the fluids examined from various gynecologic conditions were false positives so far as we can determine. The test is apparently more specific if a tiny piece (50 mg.) of the cervix is examined.

We hope that the test may be used more generally in order that its exact value can be determined within one or two years. If the test proves reliable it will not only serve as an excellent screening method but will enable the doctor to establish the presence or absence of carcinoma of the cervix by a tiny office biopsy. Thus the number of hospital admissions for cervical biopsy, with its high cost, will be decreased.

The chemical analysis of cervical tissue, especially in the carcinoma in situ cases, may enable us to decide definitely whether this lesion is carcinoma or not.

Dr. Friedman, one of our residents, has been using ultraviolet light and fluorescent stains for detecting the malignant cells in the vaginal smears. He has found certain stains which are picked up by the malignant cells. The field is black and the malignant cells fluoresce brightly. Cellular detail is more distinct.

I do not believe that a hysterectomy or irradiation therapy should be carried out because the woman has an abnormal smear by the Papanicolaou technique or by any other method until more information is available.

DR. JOHN I. BREWER, Chicago, Ill.—We were slow in taking up in our service the vaginal smear procedure. We now use it and our experience has convinced us that it is of value. I would like to discuss one case.

The patient, aged 30 years, had had no symptoms. In taking a routine vaginal smear a positive test was obtained. Four biopsies were taken from the cervix and all four were negative. Because of the positive smear, however, we continued our search. Turning the paraffin block over and sectioning the other side revealed carcinoma in one. Since we call it carcinoma we believe it should be treated as carcinoma, so we irradiated the cervix after doing a biopsy by a modified Sturmdorf amputation. The tissue was studied by serial sections. No invasion was present. One area showed carcinoma within the subepithelial layer; another which was completely separate in serial section showed abnormal epithelium and abnormal mitotic figures. In still another portion there were malignant cells and complete disorientation. Another region separate as demonstrated by serial section showed large cells with multiple huge nuclei and clumping of the chromatin. The last area in serial section was not in the edge of the malignant region but contiguous to it.

I believe the smear procedure is a good diagnostic aid, but we do not treat a patient on the basis of smear alone. A biopsy is always studied.

DR. KARL MARTZLOFF, Portland, Ore.—I would like to ask Dr. Meigs whether a sound was passed into the cervical canal of those patients with unsuspected carcinoma to see if the sounding would produce an abnormal amount of bleeding.

While Dr. Meigs' paper concerned itself primarily with the Papanicolaou technique for discovering carcinoma, he did not confine his remarks to the foregoing. I wish to direct my comments to that part of Dr. Meigs' paper not directly concerned with the Papanicolaou technique. First, I would like to object to the inclusion of these noninvasive carcinomatoid changes, generally called carcinoma in situ, under the general category of carcinoma. I think this represents loose thinking. It is getting us into an untold amount of avoidable trouble and such confusion that some teachers of obstetrics and gynecology are classifying carcinoma in situ as bona fide invasive carcinoma and they are treating them as carcinoma problems rather than problems that require further study. It is also a great mistake, I believe, to speak about carcinoma in situ in a patient who has an established, bona fide carcinoma. Obviously, many carcinomas have an area somewhere at the periphery of the tumor where there is a collateral noninvasive carcinomatoid change. The issue here then is not carcinoma in situ, but a bona fide cancer, and the two should not be confused if clarification is to come to this matter. The significance of these collateral noninvasive cancerlike areas at the periphery of some cancers is not understood. It also has not been proved that a noninvasive *(sui generis)* carcinomatoid change eventually develops into cancer, although the theory is alluring and may possibly be correct. However, that does not now justify a prophetical approach to the problem. I do not think we are justified, therefore, in treating a patient with carcinoma in situ by radical hysterectomy or a modification of the Wertheim operation merely as a precautionary procedure. If a patient has a positive Papanicolaou smear, has no area on the cervix that is suspicious, and if passage of a uterine sound into the cervical canal does not reveal suspicion of friable tissue or unusual bleeding which would indicate the propriety of gentle curettage, or if a previous biopsy has shown only a noninvasive carcinomatoid change, then I believe a conical enucleation of the cervix is indicated. We then have the canal which can be cut into numerous blocks and sectioned. If such a study fails to reveal bona fide carcinoma and if the carcinoma in situ does not extend beyond the longitudinal limits of the sections, that patient, in my experience, requires no further treatment. Still, we have all had experiences where such a clean-cut decision could not be made. The choice of procedure then becomes a matter of individual judgment.

MRS. RUTH GRAHAM, Portland, Ore. (by invitation).—I would like to leave one thought in your minds. In spite of all the lay publicity throughout the past few years, a good many of you who recognize early carcinoma of the cervix are still seeing cases in the late stages. I am sure you have all had the experience of wishing you had seen the patient six months earlier. I think perhaps we will have trained personnel in the future in central laboratories where general practitioners can send the smears they take from the posterior fornix, and if they are positive, perhaps you will see these patients earlier. It is not an office procedure; it is a procedure that takes a good deal of time and experience so it should be set up in hospitals or centers where there is well-trained personnel.

I would like to say that I think you should not ignore this test because no one can afford to disregard any method which may find early carcinomas of the cervix. When the cure rate of carcinoma of the cervix is at its present low figure, any means we can use to improve this low cure rate should be used.

DR. MEIGS (Closing).—We feel that on the whole we know very little about carcinoma in situ. We have done conization operations to cure it and we now recognize our error. We feel that some of these lesions do proceed on into invasive carcinoma. I believe that if a patient has carcinoma in situ, which I feel reasonably sure is carcinoma in situ, I would prefer to take the uterus out rather than take a chance on conization.

WHAT CONSTITUTES AN ADEQUATE CANCER DETECTION EXAMINATION OF THE CERVIX?

With Comments on the Supplementary Value of Surface Biopsy*

EMIL NOVAK, M.D., BALTIMORE, MD.

THE most important measure which can be taken by a woman anxious to protect herself from cancer is a competent gynecological examination at periodic intervals, preferably no longer than six months. This statement will seem trite enough, since it has been accepted and publicized by all who are actively interested in cancer educational campaigns, including the American Cancer Society. The developments of recent years have raised the question of what constitutes an adequate examination of the woman who is intelligent enough to present herself for this purpose.

Is it sufficient to secure a history and to make a thorough gynecological examination of the traditional type, including careful inspection and palpation of the abdomen and breasts, examination of the external genitals, careful bimanual palpation of the internal genitals, and especially a meticulous inspection of the cervix in the best possible light? If this is not considered adequate, I believe that most practicing gynecologists have been and most of them still are derelict in their full duty to the patient who presents herself for examination. Such an examination will reveal the presence of a tumor in any of the pelvic organs or in the breast, unless it is so small as to be both impalpable and invisible. As a matter of fact this simple type of examination constitutes pretty much our whole armamentarium in the detection of such common tumors as cancer of the ovaries and cancer of the breast, to mention only the malignant forms.

But in the case of the cervix, with which this symposium deals, is it not true that even a normal-appearing cervix may somewhere in its extent contain a small, invisible, impalpable and symptomless focus of preinvasive carcinoma, which at some unpredictable time in the future may embark on the invasive career of real clinical cancer? And is it not true that even very early invasive lesions have at times been found in such grossly normal cervices, and with no clinical symptoms? No one will deny these possibilities any more than one can deny that in the entirely normal-feeling breast a hidden group of cells may have already committed themselves to a cancer career. But the analogy with the breast is not complete or sound, since the cervix, unlike the breast, is to all intents and purposes an external surface accessible to more intensive investigation than is possible for the breasts.

*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16, 1949.

As regards the cervix, the purpose of periodic examinations is coming to mean not only the detection of very early clinical cancer, but also the discovery of preinvasive stages which in an indeterminate proportion of cases are at some unpredictable time followed by the invasion which in former years was looked upon as the sine qua non in the diagnosis of malignancy. The still comparatively meager material available in all the laboratories of the world will not for the present permit expungement of the adjectives "indeterminate" and "unpredictable" from the above statement. It is not surprising, therefore, that there is as yet no crystallization of opinion as to the best plan of management of cases in a preinvasive stage when, regardless of future potentialities, they do not constitute a serious immediate menace to the patient's life.

Moreover, it already seems clear that the diagnosis of preinvasive or intraepithelial carcinoma must be made with great circumspection and only after painstaking and often repeated biopsy and meticulous microscopic studies, as has been, most recently and on the largest scale, shown by Galvin and TeLinde.[1] In fifty-five of seventy-five cases in which the initial biopsy showed intraepithelial carcinoma, further study revealed definite evidence of invasiveness. The simple local excision which should cure every case of genuinely preinvasive character would fall far short of requirements in cases of this type.

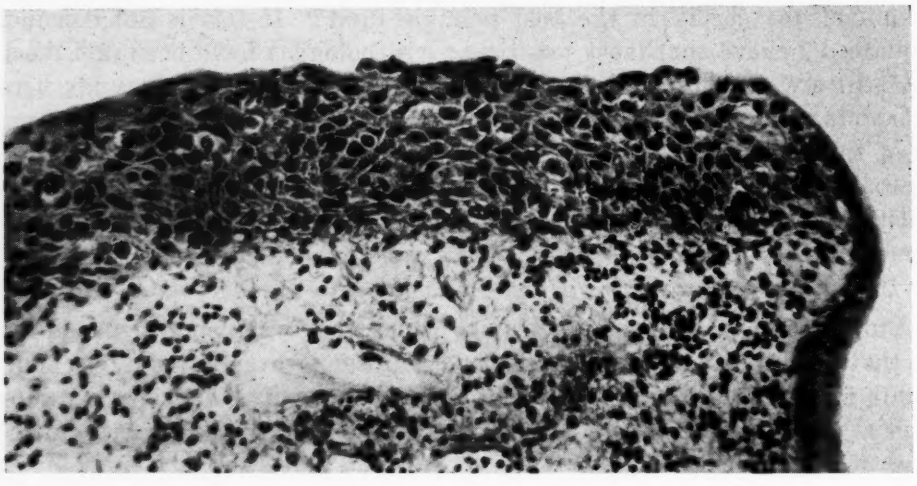

Fig. 1.—Marked epithelial overactivity in cervix of patient twelve weeks pregnant. Following miscarriage at sixteen weeks, repeated biopsies at six weeks, six months and eighteen months post partum showed complete absence of epithelial hyperactivity. (Courtesy of Drs. Louis M. Hellman and J. H. Epperson, Department of Obstetrics, Johns Hopkins Hospital.)

Vaginal cytology cannot differentiate between preinvasive and invasive lesions, and a heavy responsibility is thus placed upon the pathologist. Small wonder that some have decided that the safest procedure is to treat cases of intraepithelial cancer as cases of genuine cancer, with either radical panhysterectomy or radiotherapy. Whether the panhysterectomy is to be of the

so-called modified Wertheim type or whether it is to include pelvic gland excision need not be discussed here, as the answer to this question depends on the attitude of the individual gynecologist to the same question as regards Stage I cases in general.

To add to the existing confusion in the evaluation of preinvasive lesions, it now appears that exactly similar pictures are at times encountered in the cervices of pregnant women (Fig. 1). The role of the pregnancy hormones in producing such cancerlike pictures is indicated by the fact that in at least some cases these lesions appear to regress spontaneously after delivery. Does this mean that preinvasive cancer may at least in some cases be a reversible process? I do not believe that this question can as yet be answered with finality, and we shall probably have to grope our way along until further study clarifies the problem.

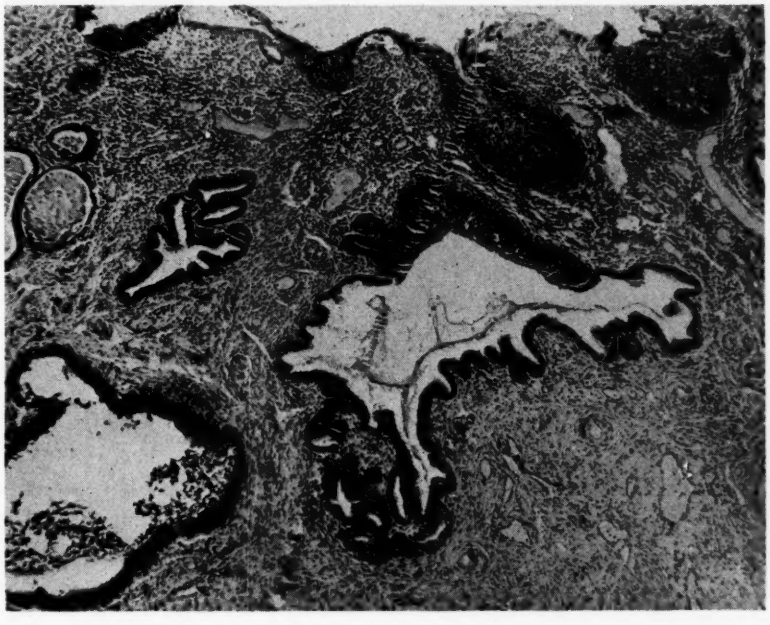

Fig. 2.—Basal budding of intraepithelial lesion, with extension along glands. This is not in itself evidence of invasiveness, although frank cancer of course does often invade or destroy glands.

Another field of confusion in the interpretation of early and precursory lesions pertains to the varying criteria as to what constitutes invasiveness. The buds which project from the under-surface of a cancerous type of epithelium are by some, if one may judge from published photomicrographs, accepted as evidence of invasiveness, even though a sharp and intact basement membrane is seen. Others feel that such pictures are produced by simple buckling of the overactive and crowded basal layers, and do not in themselves justify the diagnosis of early invasiveness, while the ever-present microscopic hazard of misinterpreting tangential sections is always with us, even when many sections are studied (Fig. 2).

Similar divergences of viewpoint are seen in the interpretation of gland invasion, which some appear to accept as definite evidence of invasiveness. However, if in the common lesion of epidermidization, a perfectly benign squamous epithelium can creep along the framework of glands far beneath the surface, certainly an intraepithelial carcinoma can do the same thing. Again, it is not always easy to draw conclusions on this point even on the basis of many sections (Fig. 3).

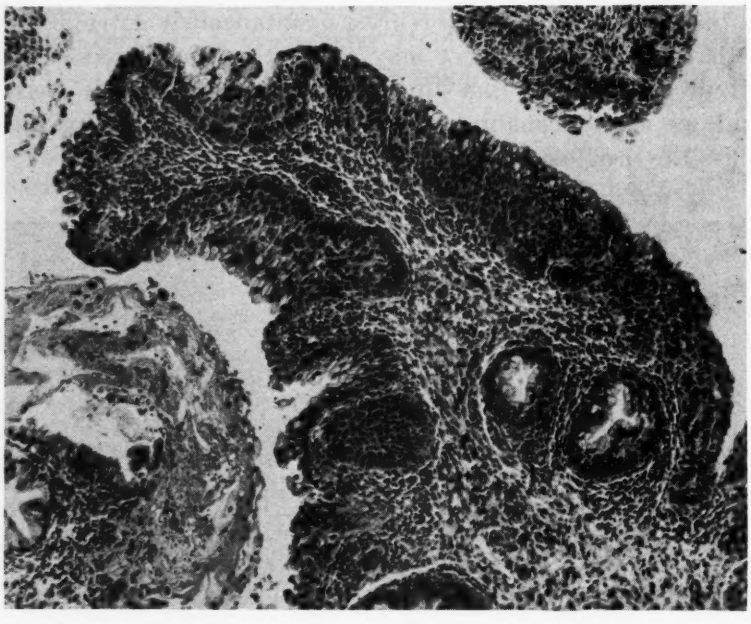

Fig. 3.—Intraepithelial carcinoma showing extension to glands.

If one can actually demonstrate a break-through of the basement membrane, with free penetration of the cancer cells, and, of course, if these can be demonstrated in small lymphatics immediately below the epithelium or in the larger ones well below the surface, there will be no difference of opinion among pathologists as to the invasiveness of the lesion (Figs. 4 and 5). But one would hesitate to say that this should be the sole criterion, and I have heard expert pathologists, like Meyer, say that in the occasional case only a sort of intuition or hunch based on long experience with such lesions must be the basis of a pathological opinion. This does not seem very scientific or helpful to the average pathologist who is called upon to make such diagnoses, but it, at any rate, serves to emphasize this particular point of confusion.

Finally, there has been much discussion of "basal hyperactivity" of varying degree as a possible evidence of epithelial unrest which, to resort to what can be considered either an absurdity or a redundancy, could be called a precursor of the precursory or intraepithelial stages of cancer. Here the fog is even thicker. Some, like Meyer, believe that inflammation is usually responsible for such pictures, while others suggest the hormonal influence which

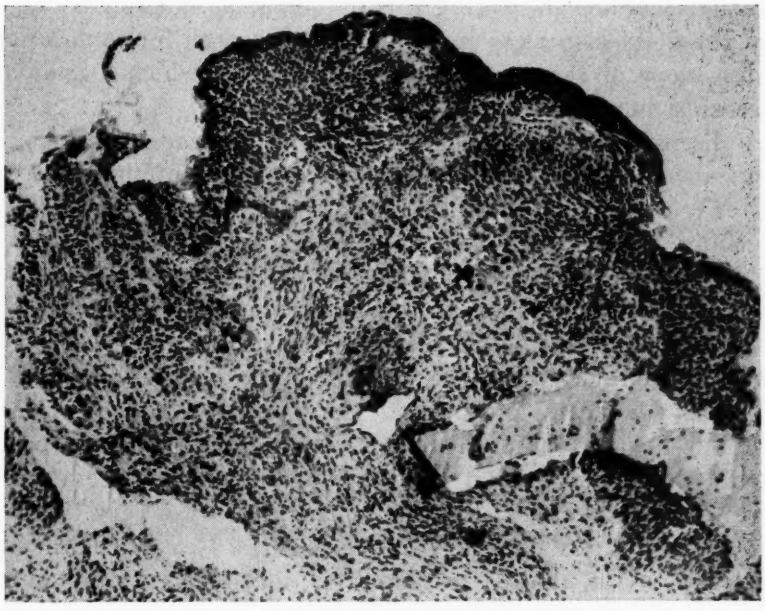

Fig. 4.—Early invasive carcinoma, with penetration of basement membrane at several points. See Fig. 5. for high power of point X.

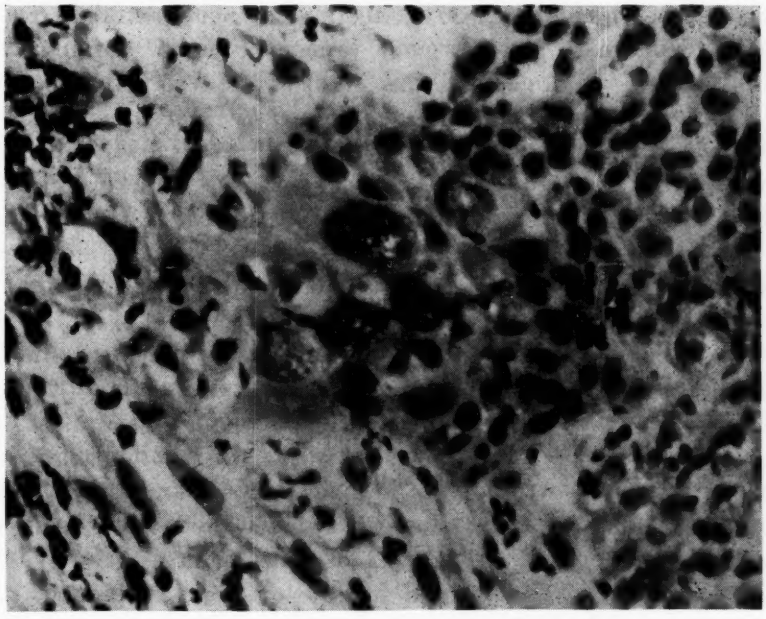

Fig. 5.—High power of point marked X in Fig. 4, showing break-through of cancer cells into stroma.

brings about varying degrees of basal activity at different cyclical phases, as I shall later discuss.

I have felt justified in making this pathological excursion, since it lies at the core of the discussion as to just how far the search for such lesions should influence the scope of the periodic examinations for which women are applying in increasing numbers.

Before discussing the methods available in the search for very early and precursory cancer, it may be emphasized that lesions of this type are highly favorable for treatment, and that preinvasive lesions may remain highly favorable for many years, and often will never become clinically cancerous. Perhaps this will comfort those clinicians who, in their examinations of women who present no such symptoms as abnormal bleeding or discharge, and who have grossly normal cervices, feel justified in assuring such patients that there is no cause for apprehension. This, I believe, has been the practice of all of us until the past few years, and I do not think it requires any smugness to feel that this policy has not inflicted any noteworthy hazard on the patient.

It should be borne in mind that the subclinical and preinvasive lesions which have received so much attention constitute only a very tiny proportion of all cancer cases. If the clinically favorable Stage I cases, embracing those in which the lesion is still limited to the cervix, make up only something like 10 per cent of all cancer cases as they present themselves, then certainly the subclinical group, including the preinvasive, can comprise only a fraction of 1 per cent. And yet they have in recent years been discussed and publicized far more than the clinically early and favorable lesions which are so much more common and which are readily detectable by simple clinical examination, plus biopsy, available to all. Has our cancer campaign gotten a bit out of balance, and are we in danger of losing sight of the woods for the trees?

The relatively uncommon, very early invasive carcinoma of subclinical type, it is true, should be curable in almost all cases by either surgery or radiotherapy, but almost the same statement can be made of the readily detectable lesions of small size, perhaps not over 1 cm. in diameter. As for preinvasive lesions, there is still much confusion as to their significance and proper management. If they are genuinely preinvasive, they should be invariably curable by simple excision, and in a number of reported studies, such as that of Stevenson and Scipiades,[2] cases of this type have remained well for many years, following even simple excision of the lesion.

I am sure that most of us have often, in the course of Manchester operations, amputated cervices which showed only such gross abnormalities as innocent-appearing erosions, without preliminary biopsy, and that the latter has often been omitted before other simple cervical procedures, such as trachelorraphy, conization, or cauterization. If any one distorts the above statement as anything like a blanket approval for the omission of biopsy before conservative procedures, I shall be highly indignant. No conscientious gynecologist would think of performing such operations without preliminary biopsy if the patient has had even the slightest bleeding, or if the cervical lesion presents such suspicious features as induration, undue granularity, or vascularity.

But if a normal-appearing cervix can harbor an early invasive carcinoma, certainly the same is true of the cervix with grossly mild pathological features, although reports of unfortunate postoperative developments due to the omission of biopsies in such cases are rare. This may be partly explained by the fact that tiny preclinical malignant foci may be actually cured by limited excision or destroyed by the cautery.

In any event, it must confuse many gynecologists to decide how far they can and should apply in their daily practice, and especially in the periodic examination of ostensibly normal women, the newer techniques which will unquestionably help to unearth an occasional subclinical lesion of either intraepithelial or invasive type. I do not know how many would go as far as Frank, who, in a very recent paper,[3] speaks of "the somewhat hysterical overanxiety to ferret out cervical cancer in situ or often only in prospect," and deplores the picture of "women racked by unjustified fears, anxieties, and premonitions of disaster caused by the witch-hunter attitude of the professional cancer tracker." He also quotes Julius Heyman, the director of the well-known Radiumhemmet in Stockholm for something like thirty-three years, as stating that "a carcinoma has never developed in a patient in whom we failed to diagnose the cancerous lesion on clinical examination or on biopsy. There seems to me thus to be some slight discrepancy between the experience of the cytologist and the clinician."

When men of such mature experience and high standing express such an attitude, the average practicing gynecologist may be left confused. Is he or is he not culpable if he does not make routine use of vaginal smears and/or biopsy in the periodic examination of ostensibly normal women with ostensibly normal cervices? He is fully aware that in such cases an occasional subclinical lesion might thus be revealed by methods which too often are not available to him, or which are simply not feasible in the routine of his daily work. But the application of new knowledge and new methods to conditions of actual practice must include considerations of realism and practicability, and it is a discussion of this point which furnishes the incentive for this paper.

Various authors have called attention to the utter impracticability of a general adoption of the vaginal smear method because of the paucity of qualified cytologists. In an excellent paper Foote and Li[5] estimate the incidence of cervical carcinoma in women over 35 years of age as 1 in 1,500, so that, since at least two slides should be studied and an average minimum of ten minutes is required for each, at least 500 hours of microscopic study is required to reveal one carcinoma. Is it wise, therefore, to incite among women a widespread demand for a method which cannot be adequately supplied at the present time? A course of a few weeks' instruction does not qualify one as a reliable vaginal cytologist. In a recent paper by Fremont-Smith, Graham, and Meigs,[6] themselves ardent champions of the method, the statement is made that "reliance on a diagnosis, for or against cancer, submitted by an inexperienced cytologist constitutes malpractice as surely as does the performance of a major operation by an inadequately equipped surgeon." They also state

that adequate cytological training requires months of intensive training and constant use of the method. The suggestion made by some that large numbers of technicians be trained to carry on the bulk of this work has thus far excited no noticeable enthusiasm, and it seems doubtful that it will in the foreseeable future.

To subject every patient examined by every gynecologist to either vaginal smear, much less biopsy, might seem ideal, but it is fantastically unrealistic in view of the fact that there is only a handful of really competent vaginal cytologists in the country, and that the larger body of tissue pathologists, something like 1,500, could not possibly examine more than a fraction of the biopsy material with which their laboratories would be swamped. These comments apply to practice in the consulting rooms of gynecologists and general practitioners, and not to cancer detection clinics or out-patient clinics with sufficient laboratory facilities and personnel to do not only routine vaginal smears, but also routine biopsies. It will thus be seen that I am trying to draw some sort of a line between what is practicable in private practice without risk of overlooking lesions in a still very favorable stage, and what should be done in cancer detection clinics which are properly equipped to study this clinico-pathological research problem.

The consulting rooms of a practicing gynecologist are not, as a rule, ideally suited for scientific investigations which require extensive and sometimes tedious laboratory study, but the out-patient departments of well-conducted hospitals, especially those of the larger teaching clinics, are equipped for such purposes. The same statement can be made as regards many of the now numerous cancer detection clinics throughout the nation. I submit that it is in such clinics that a concerted effort should be made to explore fully the potentialities of such screening methods as vaginal cytology. The soundest and most experienced students of this diagnostic procedure seem to have reached general agreement that it has no decisive diagnostic value, but that it is of great value as a screening test. Let them explore its possibilities to the utmost, and let their workshop be those clinics with personnel and equipment adequate for the purpose. There are some who have been wrongfully suspected of a reactionary attitude in so far as vaginal smear diagnosis is concerned, because they still feel uncertain about the future of the method, because they believe it possible that its value has been rather disproportionately accented and publicized, that it is being employed and unauthoritatively evaluated by some who must be considered to be inadequately trained in this not so simple procedure, and that they are fearful that too much concentration on this method will result in a neglect of the more decisive, tried and true method of biopsy in the diagnosis of cervical cancer.

It should not be forgotten that many of the results reported in the literature of positive smear findings in cervical cancer have included preponderating numbers of cases in which the smear was not at all essential for diagnosis, which in some could have been made with reasonable accuracy by simple inspection, and in others with great accuracy by biopsy. The smear technique

in such cases was done as a supplementary method, for the laudable purpose of familiarizing the examiner with the appearance of exfoliated cancer cells, but this fact should be borne in mind in comparing the diagnostic values of cytological study and biopsy. Everyone agrees that cancer is an exfoliative lesion, and that in the grossly unsuspicious cervix the finding of unquestionable cancer cells should be the stimulus to intensive and more decisive diagnostic study. But this is a part of the screening process, and no one will question the applicability of vaginal cytology in this limited but very important field. But in the presence of a clinically suspicious lesion of the cervix, I for one would consider it a far greater dereliction to omit direct biopsy of the lesion than to omit vaginal smear study. I do not think that Warren's[7] estimate of more than 99 per cent of pathologic accuracy in biopsy is at all excessive. It will be admitted that as a screening procedure the vaginal smear offers certain definite advantages over biopsy. The latter is not nearly as simple, and, even if done at various portions of a cervix which presents no target lesion, is likely to be a random procedure, which may still miss a small subclinical cancer focus. Furthermore, it is a more pretentious procedure and in many cases its proper performance calls for a light anesthetic.

It is in cases of this general type especially that I believe that surface biopsy of the cervix is of great value. The method is an old one, having been suggested by Schiller[8] as far back as 1928 and having no doubt been employed before and certainly since then by various gynecologists and with various techniques. Schiller's suggestion met with very little response, probably because of the skepticism of many at that time toward a method which could not be expected to give information as to the invasiveness which many then felt was essential for the diagnosis of cancer. It is not to be confused with the cervical smear advocated by Ayre and others, as this is only an adaptation of the cytological method, the smear being filmed and stained like the ordinary vaginal smear.

More recently Ayre[9] has recommended a species of surface biopsy performed with a so-called cone knife, the procedure being essentially a superficial scalpel conization. A somewhat similar procedure has been employed by Scheffey,[10] and no doubt by others as well. Ayre states that his method is often followed by moderate bleeding, so that it is often followed by electrocauterization. Still others recommend more extensive conization for the purpose of securing tissue for study, although this is a much more pretentious procedure than simple surface biopsy, and does not always yield satisfactory tissue for microscopic examination. Still another variation of surface biopsy has recently been suggested by Gusberg.[11] It is not my purpose to stress the superiority of any one method of surface biopsy over others, but merely to emphasize the general principle of securing for examination as simply as possible as much as possible of the surface mucosa in the area of cancer predilection.

My own interest in surface biopsy as applied to cancer diagnosis was engendered rather indirectly. In the discussion of precursory lesions there has

been frequent emphasis on various degrees of so-called basal cell hyperactivity. The more moderate degrees of this hyperactivity, it seemed to me, were possibly to be explained on a hormonal, cyclical basis, rather than being indicative of precancerous epithelial unrest. There has been almost no study of the cyclical changes in the stratified squamous epithelium of the pars vaginalis, although the studies of Sjövall have given us considerable knowledge of the histological cycle in the endocervical mucosa. While it seemed reasonable to believe that the hormonal changes in the cervical squamous epithelium would be similar to those in the vaginal mucosa, it was thought worth while to study the problem directly. Biopsy seemed to offer definite advantages over smears as a means of furnishing a comprehensive picture of the changes. It was soon found that the changes are not uniform at all parts of the same cervix, so that surface biopsy, which consists of scraping away most of the squamous epithelium surrounding the canal, was resorted to. We were pleasantly surprised to obtain long strips of mucosa, and the comprehensive picture thus obtained naturally suggested the value of the technique in the search for early or precursory cancer lesions.

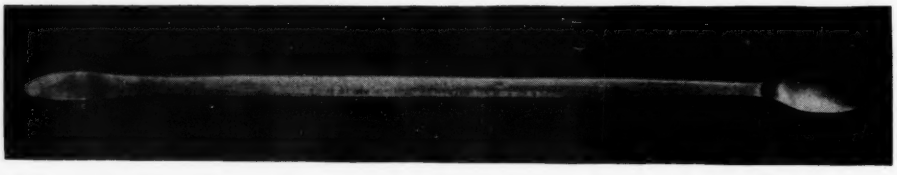

Fig. 6.—Sharp-edged, long-handled, double spoon used for surface biopsy, though ordinary scalpel is often satisfactory.

The instrument we have employed is a scalpel or a long, sharp two-edged spoon (Fig. 6). Cervices differ widely in their size, configuration, and in the degree of patency of the canal, so that sometimes the scalpel and sometimes the spoon is used. The latter, incidentally, is double, with a smaller spoon at one end of the long handle, and a larger one at the other, making easier adaptation to cervices and cervical canals of different sizes. I feel sure that some one more inventive than I can devise something even better, and we have experimented with various other appliances, but so far the scalpel and spoon have seemed most satisfactory. The entire circumference of the canal, or if this is everted, the junction of the squamous- and cylindric-celled zones, is sharply scraped, and also the endocervix just above the os. The tiny fragments are washed off the instrument in a large tube of formalin or alcohol-ether. They are not stained as a film, but the fragments are centrifugalized and then run through the ordinary paraffin technique, with hematoxylin-eosin staining. Figs. 7 and 8 give an idea as to the long strips of epithelium often obtained. Sometimes they yield practically all the circumferential epithelium, in others they are more fragmentary and less complete. Only a slight oozing surface is left, which epithelizes within a few days.

The procedure has been done as a routine in all vaginal operations during the past year or more, numbering something like 300 cases. The histological

cyclical studies will be reported later in a paper by the author, in collaboration with Dr. A. W. Lyons. That this technique has definitive value in cancer detection may be illustrated by two cases.

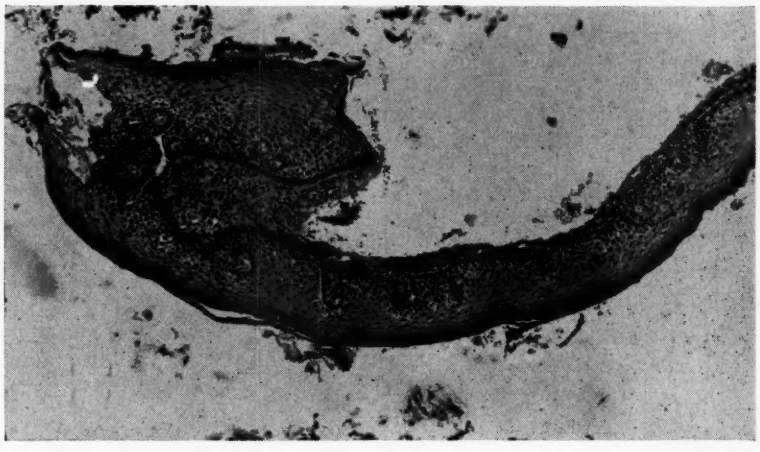

Fig. 7.—Examples of long strips of surface mucosa obtainable by surface biopsy.

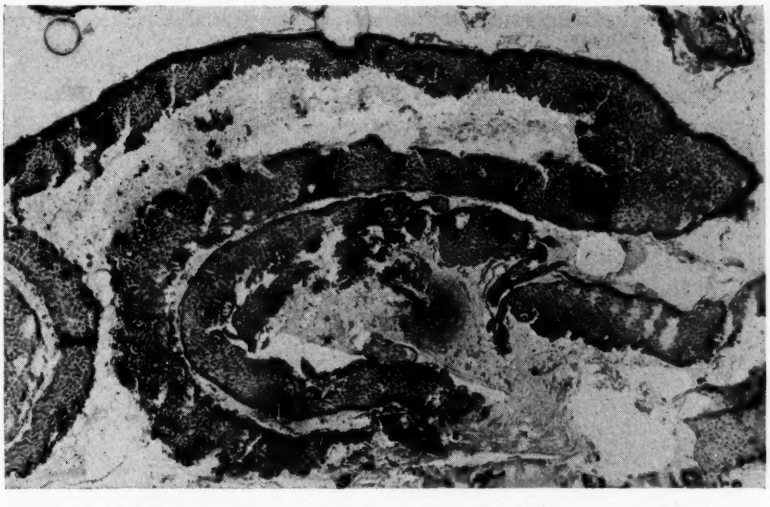

Fig. 8.—Another example of surface strips obtained by surface biopsy.

CASE 1.—F. H., aged 41 years, had slight occasional staining especially on coitus, for several months. Menstruation was somewhat irregular, with cycles of from three to six weeks, but with scantier flow than formerly, lasting two to three days. She had had two full pregnancies, with normal labors, seventeen and thirteen years ago. There were no gross abnormalities of the pelvic organs except that the bilaterally lacerated cervix showed a moderate superficial erosion, but with a small granular area on the right which bled on slight touch. This area was excised with the scalpel, and another biopsy taken at another point. In addition, a surface biopsy was done of the entire cervical circumference. The wedge biopsies microscopically showed only chronic cervicitis, but the cervical scrapings revealed the picture shown in Fig. 9.

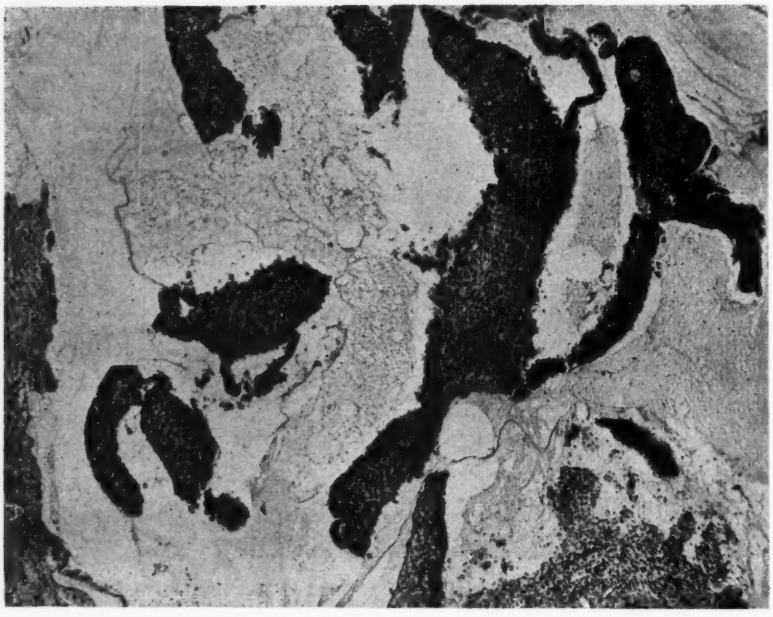

Fig. 9.—Strips of definite cancer epithelium revealed by surface biopsy in a woman 42 years old with an erosion which was slightly vascular at only one point. Punch biopsy of latter negative, but surface biopsy positive. Microscopic examination after radical operation showed very early invasive carcinoma.

Fig. 10.—Another cancer epithelial strip revealed by surface biopsy. Study of cervix after radical operation showed frank though early invasive carcinoma.

CASE 2.—P. H., aged 48 years, complained of slight postcoital stain on several occasions during the past two months. Menstruation was normal in character and amount, and there was no leucorrhea. There had been one full-term pregnancy with forceps delivery twenty-five years ago, and three early miscarriages, the last fourteen years ago. The cervix was slightly hypertrophic, with a superficial vascular area at the left angle of an otherwise not suspicious-looking erosion. Here again, wedge-excision gave negative microscopic findings, while the surface scraping yielded the lesion shown in Fig. 10.

In addition to these two cases, I have encountered a group of other suspicious lesions in which direct biopsy was positive, but in which the supplementary surface scraping threw additional light on the extent of the lesion. A recent case, for example, showed a long strip of cancerous epithelium adjoining a very small invasive lesion, as determined by punch biopsy. The study of the cervix after the radical operation which was done showed that the lesion was considerably more extensive than might have been surmised from the wedge-excision alone. The supplementary use of surface scraping, therefore, would seem to broaden the scope of biopsy even in the cases in which a definite target lesion is present.

Summary

The vaginal smear method appears to have established itself as a valuable screening test, but it is not comparable to biopsy as a decisive diagnostic procedure, nor can it distinguish between intraepithelial and invasive cervical cancer.

The possibilities of vaginal and cervical cytology should be fully explored by those fully qualified to do so, and the chief workshop for this purpose should for the present be well-organized and well-equipped clinics. There are still too many pitfalls and limitations to recommend its general adoption among practicing gynecologists.

There must still be uncertainty as to the future role to be played by cytological studies, and some justification for the feeling that their importance has been overaccentuated and overpublicized, for reasons elaborated in this paper.

There is no need for vaginal smear studies in the vast majority of cases of clinical cancer, with existing lesions, either obvious or suspicious, though there can certainly be no criticism of their supplementary employment. The omission of biopsy in such cases is far more culpable than the omission of vaginal smears.

While intraepithelial carcinoma is now commonly accepted as a precursor of invasive cancer of the traditional clinical type, there is still much uncertainty as to the chronological and histological relations between the two. The lack of crystallization of opinions as to the therapy of intraepithelial carcinoma is understandable in view of our still meager knowledge on these points.

Only about 10 per cent of clinical cancers are in the favorable Stage I, so that there is still a tremendous need for the education necessary to enlarge

this group. The precursory lesions thus far revealed constitute a numerically tiny group, and they appear to be receiving a disproportionate amount of the educational effort. Is our cancer campaign getting a bit out of balance?

The study of lesions believed to be precursory to clinical cancer, especially intraepithelial cancer, is of intense interest, and has great scientific potentiality. On the other hand, it is my opinion that at the present time the lives of many more women will be saved by an intensification of our efforts to increase the proportion of Stage I cases than can be saved by the search for cancer in this preinvasive form.

It is difficult at this time to predict whether or when vaginal cytology will ever become a generally available diagnostic aid. Until such time, which does not appear to be in the very near future, the practicing gynecologist who makes full and conscientious use of universally available methods, including biopsy in the presence of even very small suspicious lesions, will not miss many cancers in a still highly favorable therapeutic stage.

In the screening field, vaginal cytological methods offer definite advantages over biopsy, even of the multiple type, but smears in themselves should not be made the basis for treatment. The limitations of biopsy in women with ostensibly normal cervices can be largely overcome by some such method of surface biopsy as that described in this paper. It is recommended as a valuable procedure, especially in cases where the cytological smears have been positive.

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Discussion

DR. NEWELL PHILPOTT, Montreal, Quebec.—We agree that the actual tissue section is the best positive approach to an accurate diagnosis. At the same time Dr. Novak has emphasized the duty of larger teaching centers to investigate the combined approach of a cytological screening with corroboration by a surgical biopsy. We also endorse the statement that cytological diagnosis should be made only by adequately trained personnel and that the technical staff be capable of preparing slides which are diagnosable.

I am in a position of being able to discuss the virtues and disadvantages of the surgical biopsy in comparison to the cytological diagnosis from surface scraping. This is due to the fact that I am frequently called upon to act as referee in a spirited controversy where my Department of Gynecological Pathology does not agree with my Cytological Department.

There are a few points where my opinion varies somewhat with that of Dr. Novak. With reference to cellular changes of the cervix in pregnancy, I should like to state that we

have completed a study in 1,500 cases at different stages of pregnancy. We have found marked secondary hyperplasia which some may term precancer cells, but this should not be confused with the true cancer cell.

In our clinic we place more reliance upon the cervical scraping than upon the vaginal smear. We believe that these scrapings will usually indicate a type of cell change in morphological and staining characteristics which will lead one to suspect or discount the possibility of invasive cancer. Of course, this should be corroborated by surgical biopsy. We think that the so-called intraepithelial lesions can be followed with more safety by means of repeated cytological studies than by the repeat punch biopsies which may be harmful. And, although we are doing ring biopsies of the whole squamocolumnar junction in order to obtain multiple sections, we are not satisfied that this procedure is to be recommended wholeheartedly except for accurate diagnosis.

I should like to ask Dr. Novak if he thinks that preclinical cancer is very rare because a biopsy is taken too infrequently. Since the advent of cytology smears we have had a tremendous increase in incidence. In the last three and a half year period we examined 7,830 cases; 106 of these cases should be classed in the preclinical group of cancer of the cervix; 41 were diagnosed as preinvasive, and all cases had a corroborating pathological diagnosis.

In an article published from Mengert's Clinic by Diddle and collaborators, it states: "Since routine cytology tests were done in the last twenty months almost as many noninvasive carcinomas of the cervix were discovered as were found in the preceding ten years."

Results in our "Well Woman Clinic" show that cervical cancer rarely occurs without some clinical manifestation, but the situation is very different in our general gynecological outpatient clinic. All these patients have symptoms of trouble, and many present what Dr. Novak so well describes as grossly mild pathological features, such as a catarrh or an erosion of the cervix. In this type of patient the cytology smear has proved invaluable. Since routine smears have been the procedure for a two and a half year period, most cases were accurately diagnosed clinically. However, in a total of 4,000 cases of patients who presented themselves, fourteen individuals were examined by competent members of my staff and the patients sent home. They were given instructions for treatment and were told to report at a later date. The cytology report which was presented twenty-four hours later gave positive findings. Nine of these cases were proved to have invasive cancer and the other five were of the intraepithelial type. These were definite "misses" on the part of the clinician.

We are all agreed that cancer can be cured only if it is treated in the early stages. Surely more emphasis should be placed upon the developing of a system to make this early diagnosis possible. The results would be more gratifying and would have less tendency to cause cancer phobia than our present approach of late diagnosis and treatment by spectacular but disappointing means such as pelvectomy, the Wertheim operation, or massive radiation therapy.

An adequate clinical examination is basic. Our recommendation is that cytology be coupled with this initial approach. Cytology is an excellent screen and gives a lead to further search. However, it cannot at present be taken as final or as a basis for active treatment. The surgical biopsy gives a comprehensive picture if taken from the offending area. In so-called preclinical cancer it is usually a difficult task to find this elusive area. In addition, repeat biopsies are traumatizing and may cause spread of an existing cancer.

DR. J. ISFRED HOFBAUER, Cincinnati, Ohio (by invitation).—The morphologic appearance of the manifestations of hyperplasia and metaplasia of both the surface mucosal epithelium and the glandular cervical epithelium with well-defined ingrowths and hyperchromatism during gestation was fully detailed in a paper published in this JOURNAL in 1933 (Vol. 25, No. 6). It was suggested that "the production of solid tongues of proliferating epithelial cells in the cervical mucosa may represent an important link in the chain of causative factors for the later development of malignancy. As an important element in cancer prophylaxis, proper inspection in the postnatal clinic of the cervical tissues and immediate attention to any vascular or granular area seems imperative." The inciting causes of the hyperplasia and metaplasia of the cervical epithelia incident to gestation were determined

by the experimental production of such cervical lesions by the oversupply of anterior pituitary and ovarian hormones (see this JOURNAL, Vol. 27, No. 5), and the specific response of the cervical epithelium to hormonal stimulation was duly stressed.

DR. JOHN W. W. EPPERSON, Baltimore, Md. (by invitation).—Studies of the pregnant cervix have been made with a punch biopsy forceps during the past year. No cervical or vaginal smears have been done but it is expected to continue this study by these other methods in the near future. At the present time a total of 290 patients have been biopsied during pregnancy and the puerperium. A total of 780 biopsies have been obtained without an increase in the rate of abortion, stillbirth, or premature labor.

Of the biopsies obtained prenatally, 15 per cent have hyperactivity of the basal layer of the stratified squamous epithelium. Six patients have had a diagnosis of intraepithelial carcinoma of the cervix, which was confirmed by competent pathologists throughout the United States. Of these six patients all were normal in the postpartum period. Two patients were followed eighteen months, two have been followed six months, and one patient was followed five months. All of these patients continue to have normal biopsies. One patient did not return to the dispensary after her first postpartum visit and has not been followed. Of the patients with basal cell hyperactivity during pregnancy, 85 per cent were completely normal in the fourth postpartum week.

DR. NOVAK (Closing).—In his discussion Dr. Philpott alluded to the possible harmfulness of surface biopsy, but I cannot conceive of any element of harm in the procedure. The raw surface left is smoothly epithelized within a few days, and only occasionally is it necessary to touch up an oozing area with the cautery point. It is precisely in the group of cases mentioned by Dr. Philpott, in which the absence of a target lesion makes scalpel or punch biopsy a rather random procedure, that surface biopsy would seem to have its clearest indication. No intelligent person will criticize the use of vaginal smears when these are properly evaluated, and not in themselves made the basis for decisive treatment. But one cannot avoid a feeling of irritation in reading some of the articles in lay publications which do not make clear the limitations of the method, as well as its unavailability to all but a small fraction of the women of the country.

A STUDY OF 135 CASES OF CARCINOMA IN SITU OF THE CERVIX AT THE FREE HOSPITAL FOR WOMEN*†

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THE concept that carcinoma in situ of the uterine cervix is a preinvasive stage of cervical cancer has been considered for many years. Definite proof that this concept is valid has yet to be presented. The questions which must be answered to prove the validity of this controversial subject are: 1. Does the disease occur at a regular rate consistent with the incidence of undoubted cancer of the cervix? 2. Is the average age incidence consistently less than that for invasive cancer? 3. Is the disease an irreversible process? The experience with noninvasive carcinoma of the cervix at the Free Hospital for Women for a period of nearly twenty years can answer the first two questions and shed light on the third.

Review of Literature

In 1912, Schottlaender and Kermauner[1] described the surface coating of malignant epithelium (Fig. 1*A*) at the periphery of invasive cancer (Fig. 1*B*). I. C. Rubin,[2] a student of Schottlaender, in 1910, reported three cases of "incipient carcinoma" of the cervix. Rubin's first two cases, as he described and pictured them in drawings from serial sections of the whole cervix, were examples of carcinoma in situ with extension into the cervical glands. A radical hysterectomy was performed on the first case, and the iliac and hypogastric lymph nodes were negative. His third case probably represented "epidermoid hyperplasia" in a prolapsed cervix. Rubin's question, nearly forty years ago, presents the problem as it exists today: "What shall we regard as metaplastic, nonmalignant, epithelial changes, and what shall we regard as typical carcinomatous epithelium, or an atypical epithelium that will sooner or later develop into a full-fledged carcinoma?" Rubin concluded, "The important criteria of malignancy in these early cases lie not so much in the relation of the cell nests to the stroma, the depth or extent of epithelial invasion, or evidence of surrounding inflammatory changes, as in the intrinsic morphology of the epithelial cells."

Cullen,[3] in 1921, published a report of an unsuspected case of early cancer of the cervix which has been considered in the literature as one of the earliest reported cases of carcinoma in situ. From Cullen's description and photomicrographs his case is an early invasive cancer. His paper, however, did much to stimulate interest in finding more cases similar to Rubin's. Seventeen years after Rubin's paper, one of Kermauner's students, Walter Schiller,[4]

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†Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

published his first description of what he called "beginning carcinoma" of the cervix. He believed that these noninvasive lesions were definitely carcinoma. In 1932, Broders,[5] under whom one of the authors studied (P. A. Y.), introduced the term "carcinoma in situ" which has been used since 1936 in this clinic. The same cervical lesion frequently is described by other terms, such as, "noninvasive potential carcinoma," "Bowen's disease of the cervix," "incipient carcinoma," "preinvasive carcinoma," and "superficial noninvasive intraepithelial carcinoma," or just "intraepithelial carcinoma." For purposes of clarity this histological entity will hereafter be referred to as carcinoma in situ.

Since 1933, numerous papers have been published on the microscopic picture of carcinoma in situ and the minimal criteria necessary for the diagnosis of this preinvasive stage of cervical cancer. On the other hand, there have been very few reported cases that have been followed without treatment which is the only way to determine the exact potentialities of this disease. The work of Pemberton and Smith,[6] who first reported this type of follow-up study in 1929, will be discussed in detail later. Others who have found carcinoma in situ progress to invasive cancer in addition to Smith and Pemberton's[17] four cases are: Schiller,[7] three cases; Stevenson and Scipiades,[8] two cases; Younge,[9] two cases; Knight,[10] two cases; Schmitz and Benjamin,[11] one case; Rubin,[12] one case; Goldberger,[13] one case; Taylor and Guyer,[14] one case; Pund and collaborators,[15] one case; and Te Linde,[16] one case —a total of nineteen cases.

Te Linde's patient died of metastatic carcinoma of the cervix six months after irradiation therapy for carcinoma in situ. A reasonable doubt, therefore, exists in our minds that this case had only carcinoma in situ at the time of her treatment. The same doubt exists for one of Smith and Pemberton's[17] cases. Also one of the cases reported by Younge[9] in 1939 has been excluded because we do not agree now on the diagnosis of the original biopsy specimen.

In this paper two hitherto unreported cases will be cited in which carcinoma in situ progressed to invasive cervical cancer. Thus, at the present time, there are only eighteen such cases in the literature.

Experience at the Free Hospital for Women

In 1929, Pemberton and Smith[6] of the Free Hospital for Women reported three cases of carcinoma in situ of the cervix among sixteen cases of unsuspected cervical carcinoma. One of the cases was diagnosed incorrectly as benign at the time a trachelorrhaphy was performed. When, however, this patient returned four years later with invasive cervical cancer the slides were re-examined, and the diagnosis of carcinoma in situ was made. This patient upon whom the trachelorrhaphy was performed in 1916, and who died of cancer of the cervix in 1920, is the first case in which carcinoma in situ unwittingly was observed to progress to infiltrating cancer. That same year, 1929, an additional case of carcinoma in situ was discovered in an amputated cervix by Dr. Pemberton. The slides were sent to Drs. Frank B. Mallory and James Ewing. Dr. Mallory wrote: "My opinion on No. 16780 is as follows: More or less dilatation of cervical glands, some of which contain mucus and polymorphonuclear leucocytes; infiltration of the submucosa with many leucocytes and plasma cells and a few eosinophils; extension of the squamous epithelium covering the surface for some distance into some of the glands; marked proliferation of the epithelium; mitoses very numerous. It evidently does not mean malignancy. The unusual feature in your case is the marked proliferation of the

epithelium. This may be due to injury by some chemical, for example, iodine, followed by active regeneration. Diagnosis: Chronic cervicitis."

The above quotation is a good objective description of carcinoma in situ by a famous pathologist who insisted upon invasion as one of the criteria for the diagnosis of carcinoma. Also, it is interesting to note that Dr. Mallory did not mention the aberrant location of the mitotic figures and the loss of differentiation, histological features which characterize carcinoma in situ.

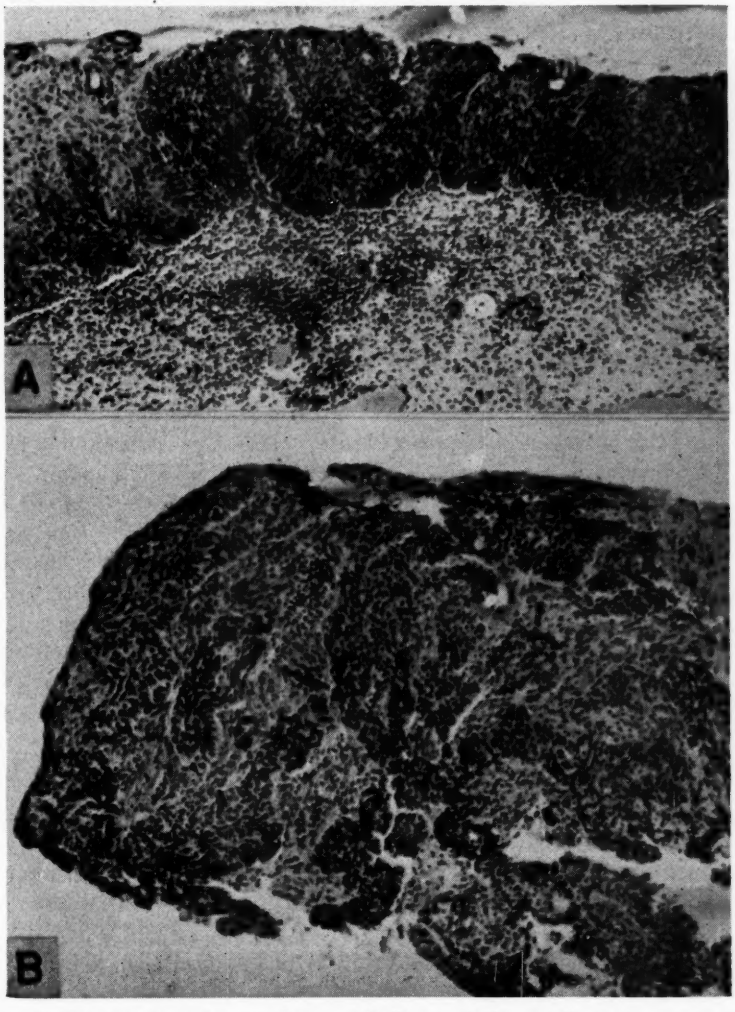

Fig. 1.—*A*, The noninvasive surface epithelium of the portio from a case of clinically evident squamous carcinoma of cervix. The normal portio epithelium is on the left and the malignant, but noninvasive, neoplastic epithelium is on the right. Note hyperchromatism and lack of differentiation. (This "surface coating," at the periphery of definite cancer, was first noted by Schottlaender and Kermauner, S-43-2414.) (×100.)

B, Typical squamous carcinoma from same case as seen in *A*, S-43-2516. (×150.)

Dr. James Ewing on the same case wrote to Dr. Pemberton: "I am inclined to agree with you that the cervix slides you sent me show beginning carcinoma. It is very early, shows no definite infiltration, but the cell layer is much thickened, and the cells show marked hyperchromatism. They look like cancer cells. Kermauner has described just such superficial, wide-spread

cases of early cervical cancer. Now early beginning cervical cancer is not true cancer in the clinical sense, so don't you go to work and take out this woman's uterus. All that is needed is a smart dose of radium in the cervical canal. This type of lesion is apt to run well up the canal. I am further pleased at differing with my good friend Mallory." Although the patient's cervix had been amputated, a "smart dose of radium" (3,300 mg. hours) was given, and she was alive and well fifteen years later.

The same slide was shown to seven pathologists at a meeting of the New England Pathological Society in 1938, and six of them thought the case was definitely malignant.

Between 1929 and 1934, three patients, upon whom trachelorrhaphy had been performed three to twelve years previously, returned to the Clinic, or were reported to us from other hospitals as frank cancer of the cervix. These cases, whose original slides were diagnosed incorrectly and later changed to "early cancer" (carcinoma in situ) resulted in the writing of "The Picture of Early Carcinoma of the Uterine Cervix" by Smith and Pemberton[17] in 1934. Four* of the sixteen cases reported developed clinical cancer three, four, six, and twelve years later. Six of their sixteen cases are excluded from this series after re-examination for the following reasons: four cases showing definite invasion, one anaplasia, and one with insufficient epithelium for diagnosis. The last patient developed carcinoma twelve years later and although the original cervical biopsy shows a definite carcinoma in situ pattern, the two fragments of surface epithelium are too small to be conclusive.

In 1931, a trachelorrhaphy specimen (Path. No. 18737)[9] was examined by Dr. George Van S. Smith who thought it was suspicious and probably even malignant. In deference to the opinion of other pathologists in similar cases, he committed himself to diagnosis of "chronic cervicitis." This patient's cervix was cauterized in the Out-Patient Department twice during the next two years. In 1934, three years and four months after the trachelorrhaphy, a biopsy showed definite invasive carcinoma. In spite of radium and x-ray therapy at this time, she died of generalized metastases in January, 1939, eight years and three months after the trachelorrhaphy. An autopsy confirmed the diagnosis. At the present time, our opinion of the original slide is that it shows only the minimal criteria to substantiate the diagnosis of carcinoma in situ because there is so little epithelium present. Also, we cannot be certain that it was not an invasive cancer in 1931, but the only tissue we do have shows two small areas of carcinoma in situ.

Having discovered the above case in 1934, shortly after Smith and Pemberton's paper was published that same year, we were convinced more than ever that carcinoma in situ was the early stage of cervical cancer. The experience with these cases was the foundation for our interest and knowledge of this disease.

In 1936, the diagnosis of carcinoma in situ was made on a biopsy specimen (Path. No. 26609). Dr. Frank B. Mallory made the diagnosis of "nonmalignant reparative process"; a second pathologist, Dr. Shields Warren, as "nonmalignant although precancerous"; and three other pathologists (Tracy B. Mallory, George Kenneth Mallory, and Frederic Parker, Jr.) agreed with us. One of those agreeing with us wrote that the slide was so extremely suspicious that he would not dare to report it as nonmalignant. He added that he did not feel a strong enough conviction, however, to be willing to include it in any series of cured cancers of the cervix. Since this patient's cervix was thoroughly cauterized at the time the biopsy was performed, we cannot say from the experimental point of view what would have happened to that

*One of these cases was reported by Pemberton and Smith in 1929.

lesion had it not been destroyed. Although she is alive and well twelve years later, a recent biopsy shows some degree of anaplasia in her cervical epithelium.

By 1937, in spite of our experience with five patients developing invasive cancer three to twelve years later, very few pathologists at that time agreed with the opinions of Schiller, Broders, Pemberton, and Smith. It seemed necessary, therefore, to follow deliberately an untreated carcinoma in situ to discover whether the process was reversible or not.

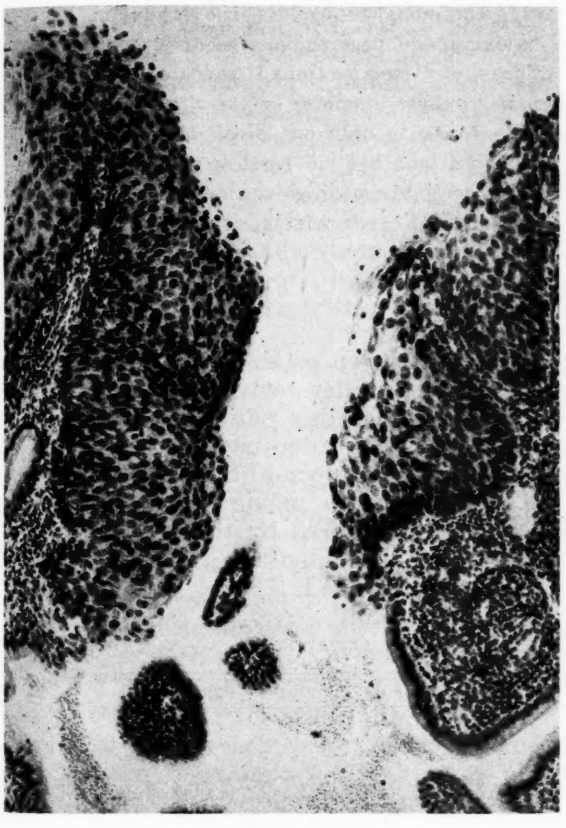

Fig. 2.

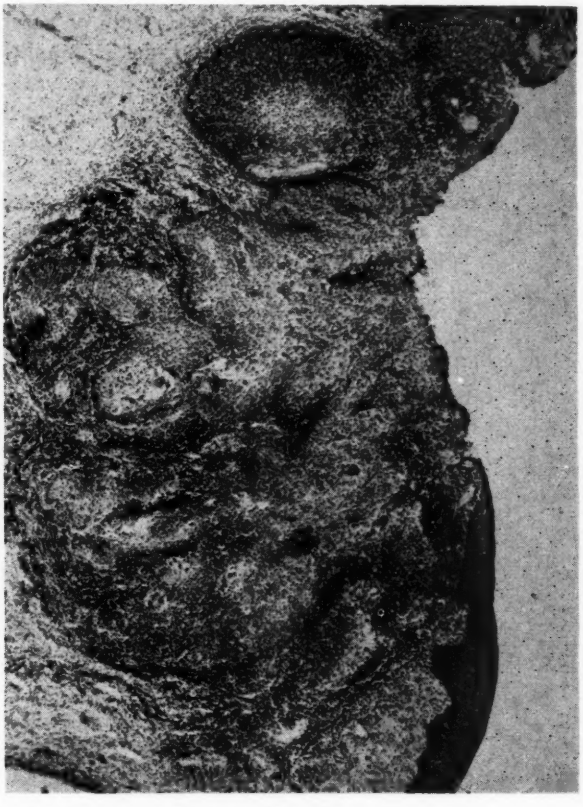

Fig. 3.

Fig. 2.—From a case of classic carcinoma in situ of the cervix with glandular involvement leading to invasive squamous carcinoma at the site of the original biopsy twelve months later. (Path. No. 27434). Original biopsy from "11 o'clock" on anterior lip of cervix. Note lack of surface differentiation, mitotic figures above basal layer, pleomorphism and hyperchromatism of nuclei. Although the malignant-appearing epithelium has involved or grown into the gland there is no stromal invasion. (×200.)

Fig. 3.—The same site from which the original biopsy seen in Fig. 2 was taken but twelve months later showing the entire squamous carcinoma measuring approximately 5 mm. in diameter. Note invasive lesion in center, glandular involvement at top and normal surface portio epithelium below on right. This emphasizes the site at which most carcinomas in situ originate in the cervix. (×70.)

On Feb. 5, 1937, a mildly eroded cervix was biopsied in the Out-Patient Department by an intern who was following the routine biopsy practice. The patient's complaints were due to trichomonas vaginitis. The biopsy (Path. No. 27434) showed a typical carcinoma in situ (Fig. 2). In the operating room the anesthetized patient was examined by Dr. George Van S. Smith. It was his opinion since the cervix was normal clinically that no treatment was necessary. Although subsequently he agreed with the pathological

diagnosis, it was decided to follow the patient without treatment because of the clinically benign cervix. In order to relieve our conscience about merely following a patient with noninvasive cancer, we decided to perform this experiment only if another pathologist *disagreed* with our opinion. Dr. Shields Warren examined the slide and gave the diagnosis of "not malignant but precancerous. Follow patient carefully." His opinion was based upon the fact that there was no evidence of invasion. Six and one-half months later a biopsy from the same area again showed carcinoma in situ, and a specimen from the posterior lip showed normal epithelium. The lesion on the right side of the anterior lip of the cervix was described as having slight increased redness of the squamous epithelium and a positive Schiller test. Eleven months following the initial biopsy, a third was taken with a curette showing fragments of carcinoma having broad pegs suggestive of stromal invasion. The cervix was amputated and serial blocks, or "step sections," revealed only a very small invasive squamous carcinoma 5 mm. in greatest diameter *at the site of the original carcinoma in situ* (Fig. 3). The cancer was found in only one block of tissue; the remaining sections showing only anaplasia. The patient had no further treatment, is alive and well, free of disease, and has a negative vaginal smear eleven and one-half years after the first biopsy. In this deliberate experiment, carcinoma in situ developed into a frankly invasive, but symptomless carcinoma in eleven months.

Material and Methods

Since that experiment ten years ago, a rule has been established in the Clinic to biopsy every eroded, everted, or positive Schiller test cervix, and determine the pathological diagnosis before treating the patient. This routine biopsy practice in the Out-Patient Clinic has rewarded us with fifty-eight (43 per cent) of the cases in this series. Forty-two additional cases were discovered by biopsy at the time of a conservative pelvic operation. Thus, 100 out of the 135 cases in this series were discovered by the routine biopsy practice. The remaining thirty-five were found incidentally following other pelvic surgery, usually hysterectomy as shown in Table I.

TABLE I. ORIGINAL DIAGNOSIS MADE FROM TISSUE OBTAINED

AT THE TIME OF	NO. OF CASES	PER CENT
Routine* clinic biopsy (ambulatory)	58	43.0
Routine biopsy at time of dilation and curettage, repair operation, pelvic laparotomy, or supravaginal hysterectomy[4]	41	30.4
Cervix from complete hysterectomy	21	15.6
Cervix from vaginal hysterectomy[1] or amputation[5] as part of repair operation	6	4.4
Trachelorrhaphy	6	4.4
Curettage for miscarriage	2	1.5
NEW PUNCH USED to obtain tissue fom normal nulliparous cervix	1	0.7
Total	135	100.0

*No. 47-4428. After three positive vaginal smears, diagnosis made from endocervical biopsy in office. Dilatation and Curettage and biopsy of cervix negative in operating room. Carcinoma in situ with early invasion at hysterectomy four months after first positive smear. This is the only case in the series in which the vaginal smear led to the diagnosis.

The fifty-eight patients diagnosed in the Out-Patient Department were studied by multiple biopsies over a period averaging forty-eight days before final treatment was performed. Most of these patients were observed by one of the authors (P. A. Y.). In addition to frequent observations and repeated biopsies, colored photographs were taken of many of these cervices between the first and second positive biopsy as well as after hysterectomy.

As stated previously, all pathological cervices are biopsied routinely, usually at 6 and 12 o'clock at the junction of the erosion and normal-appearing squamous epithelium of the portio vaginalis. Other sites are biopsied according to the dictates of a carefully performed and accurately interpreted Schiller test. This test was performed on twenty-nine of the fifty-eight patients studied preoperatively. In twenty-seven of the twenty-nine patients the Schiller test was positive and was directly responsible for the discovery of an early, usually well-localized, and curable cancer.

In spite of the utter simplicity of the Schiller test, its value is not understood by many physicians because they fail to interpret it correctly. Gram's iodine solution will stain normal squamous epithelium of the cervix and vagina a deep brown but not the columnar or metaplastic epithelium of the cervical canal or erosion. Not realizing this fact, many physicians mistakenly have regarded the *"nonstaining erosion"* as a positive Schiller test. Frequently the *nonstaining* squamous epithelium at the periphery of an erosion is just a narrow band, well localized, and it is overlooked easily as it appears to be part of the erosion after the solution is applied. Only by very accurate observation of this fact is the test of value in selecting the biopsy site. Also it must be understood that a positive Schiller test merely indicates the absence of glycogen in the cytoplasm of squamous epithelial cells and is, therefore, not a diagnostic test. Only the pathologist can say whether the nonstaining epithelium is a leucoplakia, paraleucokeratosis, or a cancer. Approximately 90 to 95 per cent of the positive Schiller tests are due to benign paraleucokeratoses, yet there is no way short of biopsy to distinguish the difference except by submitting the tissue to a well-trained gynecological pathologist.

A square-jawed punch is the most satisfactory instrument for performing a cervical biopsy for two reasons: 1. There is little danger of cutting too deeply causing serious hemorrhage. 2. More important than the occasional embarrassing hemorrhage is the fact that a square-jawed punch obtains a specimen which the personnel of the laboratory can orientate in the paraffin block so that the microscopic sections are cut at right angles to the surface. The most satisfactory punch in our experience is the Yeoman's biopsy forceps, a handmade German product unobtainable since 1940.*

All of the slides originally diagnosed up to Jan. 1, 1948, as "early cancer of the cervix," "suspicious of cancer," and "definite carcinoma in situ" have been re-examined carefully by all three authors independently. Many such cases were excluded from this series because they no longer meet our criteria for the diagnosis of carcinoma in situ either because they show definite or extensive invasion or merely anaplasia. A few cases, originally diagnosed ten to fifteen years ago, we now interpret as squamous metaplasia or anaplasia of repair. This left 135 cases of definite carcinoma in situ, an example of which is seen in Fig. 4. One hundred fifteen of the cases are typical, meeting all the microscopic criteria for this disease entity, and twenty are atypical either because of minimal surface stratification or because of the presence of many multinucleated cells (Fig. 5 *A* and *B*). There were also forty cases of probable, three of questionable, and two of possible carcinoma in situ. These forty-five equivocal cases are not included in the statistical data given in this paper but were reviewed as part of this study. Because of the presence of variable degrees of anaplasia those excluded cases are still of interest to follow since anaplasia is occasionally followed by cancer (Fig. 6) and frequently persists even after a cancer is destroyed locally.

*A good duplicate of this biopsy punch is about to be produced by Kny-Scherer Co., New York, N. Y.

Incidence

Although the number of cases of carcinoma in situ seen annually in this one clinic has increased tremendously (four in 1937 and twenty-eight in 1947), the rate of occurrence has remained constant. In the Out-Patient Department, since 1930, practically all pathological but benign appearing cervices have

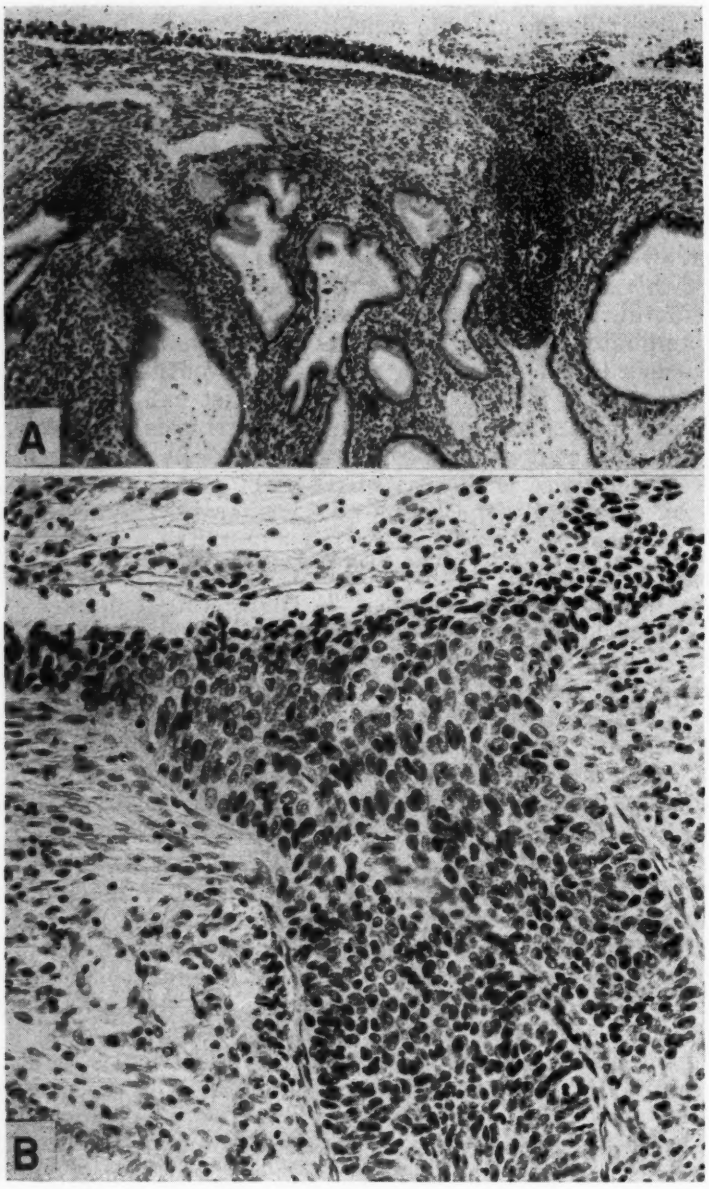

Fig. 4.—From a classic case of carcinoma in situ of the cervix showing glandular involvement. S-47-1795.

A, Low power, orienting view to show neoplasia of surface epithelium with downgrowth of latter into a gland. Note replacement of epithelium in upper half of gland. (This is not considered to be true invasion.) (×100.)

B, High power view of *A* to show cellular detail of neoplastic surface epithelium involving the neck of a cervical gland. Note lack of differentiation and desquamation of malignant cells from surface. It is significant that the vaginal smear was positive in this case. (×400.)

been cauterized and followed until healed. Fifteen years ago only those cervices which were grossly suspicious of cancer or did not heal after cauterization were biopsied, to wit, case No. 18737 (first case report). Because of this unintentional mistake carcinoma in situ was observed to progress to invasive cancer which taught us the value of biopsy before treatment and led to the deliberate experiment in 1937 (second case report). Routine biopsy then became the rule in the clinic. This procedure has furnished us with an incidence rate among women seeking aid for a variety of reasons in a large and exclusively gynecological clinic.

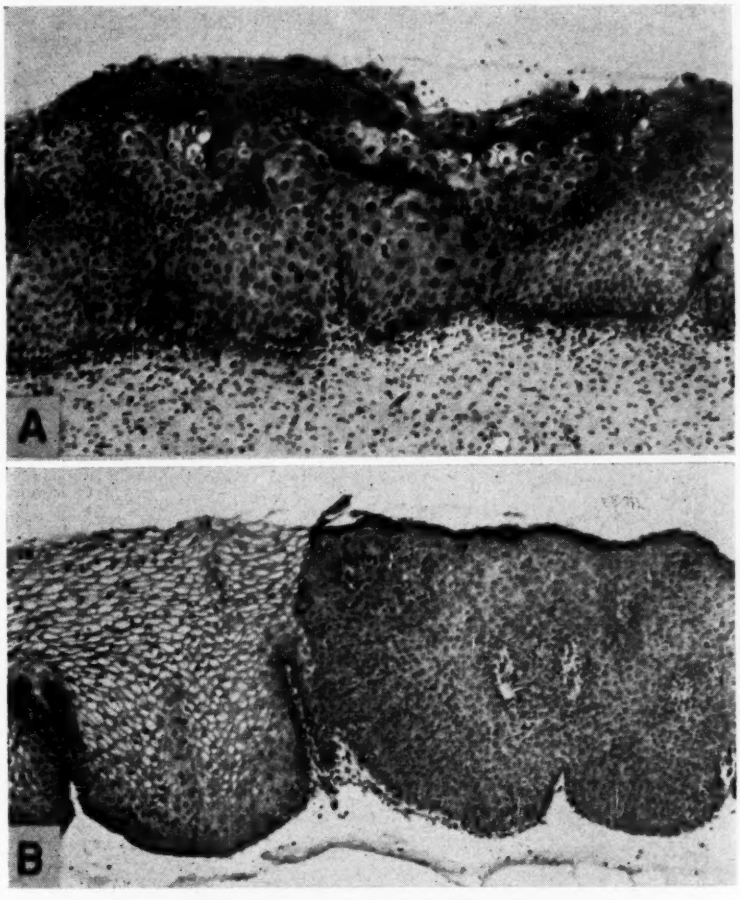

Fig. 5.—Examples of atypical carcinoma in situ of cervix.

A, A medium-power view of biopsy from portio vaginalis showing lack of differentiation, variation in cell size, and staining reaction together with the presence of multinucleated cells. S-40-2835. (×150.)

B, A medium-power view of biopsy from portio vaginalis showing slight surface keratinization but in general little differentiation. Note sharp line of demarcation between suspicious epithelium on right and normal tissue on left. Elsewhere in the cervix a biopsy showed typical carcinoma in situ. The latter was still present following hysterectomy. S-45-734. (×150.)

Thus, in 1937, 151 cases were biopsied in the Out-Patient Department, and two were found positive for carcinoma in situ (1.32 per cent), whereas, in 1946, biopsies done on 955 ambulatory patients yielded eleven cases (1.15 per cent). In our clinic, therefore, the incidence of the disease has remained at

a constant figure of about 1.2 per cent in cervices regarded as benign but diseased. It must be emphasized that our clinical criteria have been relatively constant during this ten-year period.

The incidence of invasive cancer of the cervix in a general hospital, according to Meigs,[18] is 1.6 per cent. Carcinoma in situ was found in 3.9 per cent of 1,200 clinically benign cervices examined after complete hysterectomy by Pund and Auerbach.[19] In this clinic where total hysterectomy is routine,

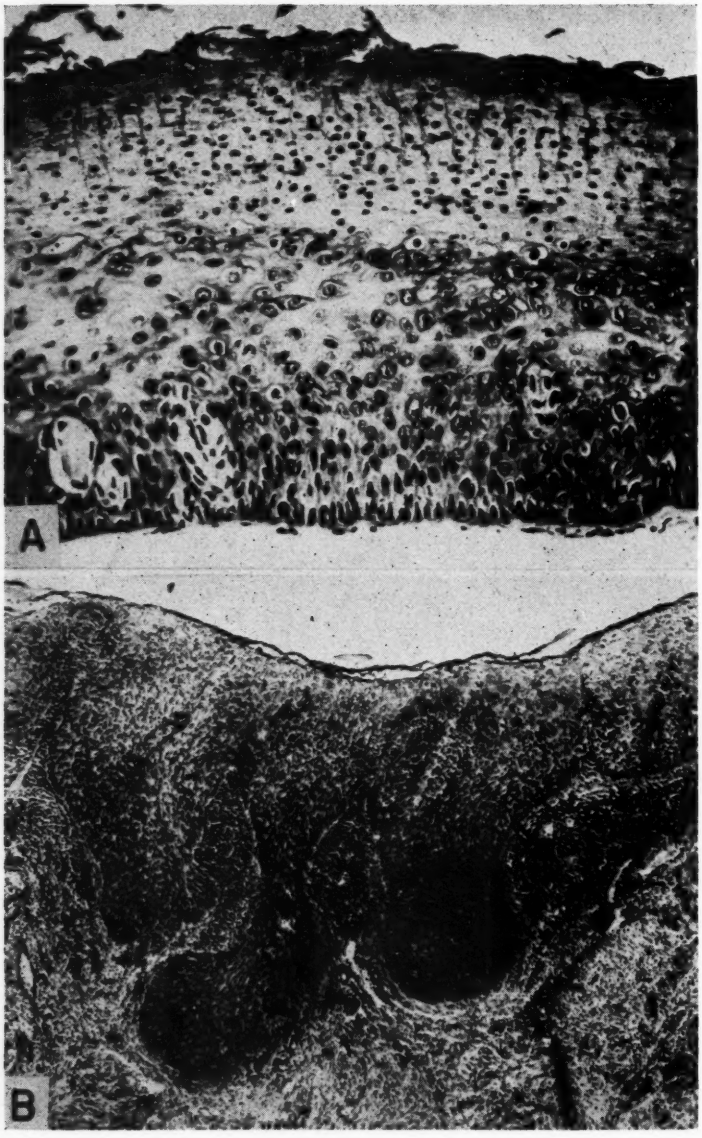

Fig. 6.—From a case of carcinoma of cervix progressing from anaplasia to stromal invasion within twenty-seven months.

A, Original biopsy showing anaplasia of basal half of epithelium but with superficial portion keratinized and moderately well differentiated. S-43-1931. (×300.)

B, Cervix at hysterectomy, twenty-seven months after original biopsy (Fig. 6 *A*) showing obvious epithelial malignancy with early stromal invasion. Note that there is some superficial keratinization. S-45-3137. (×125.)

cervical tissue from 2,262 cases was examined microscopically in 1946 (complete cervix 863; biopsy 1,399). Among the 2,262 cases there were seventy-five invasive cancers (3.3 per cent) and nineteen definite carcinomas in situ (0.84 per cent). Combining the definite with the equivocal "in situ" cases there were twenty-eight, or 1.24 per cent, a figure which approaches but does not exceed the incidence of the advanced form of the disease. The lower rate of 0.84 per cent among the total number of cervices examined as compared to 1.15 per cent among the Out-Patient Department biopsies is accounted for by the fact that many clinically normal cervices are removed by total hysterectomy whereas the Out-Patient cases are a selected group of abnormal cervices.

In this clinic, therefore, carcinoma in situ of the cervix has occurred at a constant rate for a period of ten years, and its incidence is consistent with but a little less than that for invasive cancer in a large general hospital population.

Age Incidence

Since carcinoma in situ may exist for a number of years before it becomes an invasive lesion, it is not surprising that the average age for this series of 135 cases is 38.7 years. The largest number of patients (thirty-three) occurs in the 30- to 35-year-old group (Fig. 7). Thus, the average age is 9.3 years less than the accepted average age of 48 years for frank cervical cancer.

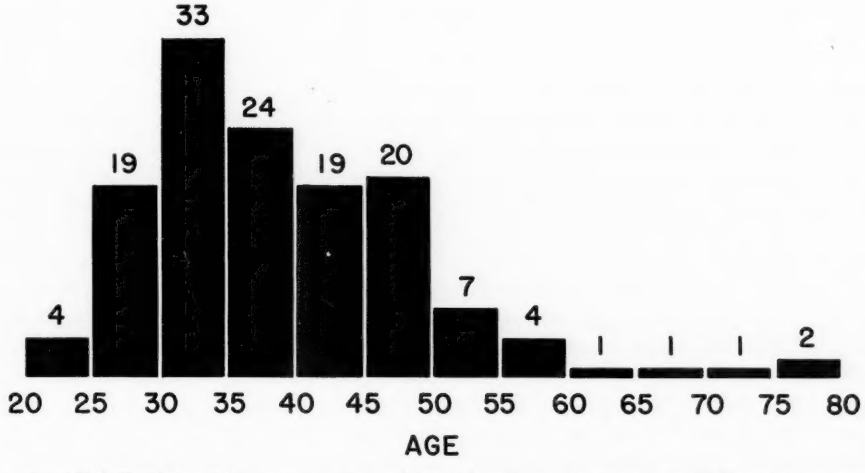

Fig. 7.—Age distribution of 135 cases of carcinoma in situ. Average age 38.7 years as compared to 48 years for invasive cancer.

Symptoms

With respect to principal symptoms, 46 per cent of the cases had no complaints referable to cervical disease. Twenty-four per cent complained of or admitted to having leucorrhea, while 30 per cent had abnormal bleeding. The latter may have originated in the cervix because it was either postcoital, intermenstrual, or postmenopausal bleeding.

Gross Appearance

While a maximum of 54 per cent of the patients had symptoms potentially referable to the cervix, only 6 per cent of the 135 cases had lesions suspicious of malignancy, that is, cervices which bled easily on manipulation (Table II). Although biopsy of all suspicious lesions of the cervix has been the teaching

for many generations, it has failed to increase greatly the cure rate for cancer of the cervix. It is not surprising, therefore, that 94 per cent of the patients in this series had cervices which were regarded as normal or benign with eversion, erosion, laceration, hypertrophy, or leucoplakia. The Schiller test proved to be invaluable in pointing out the malignant areas in many of these benign appearing cervices.

TABLE II. GROSS APPEARANCE OF CERVIX

			NO. OF CASES	PER CENT
Laceration with eversion	49			
Erosion	48	"Erosion"	107	79.3
Hypertrophy with erosion	10			
SUSPICIOUS "erosion bleeds easily"			8	5.9
NORMAL			9	6.7
Leucoplakia			5	3.7
Cervical polyp	3			
Atresia	1		6	4.4
Decubitus ulcer (procidentia)*	1			
Inadequate description	1			
Total			135	100.0

*The carcinoma in situ was on the opposite side of the cervix from the decubitus ulcer.

During the past ten years approximately 12,000 cervices have been studied clinically as well as pathologically. First, and perhaps foremost, among the impressions gained by this experience is that many of the so-called "erosions" commonly regarded as the sequelae of childbirth are, in fact, of preexisting congenital type, aggravated perhaps by the trauma of labor. Eight of the fifteen patients with carcinoma in situ who had never been pregnant had such a congenital erosion. In only one of those eight cases was the lesion suspicious because it bled easily; yet, it appeared to be a simple congenital erosion which Novak[20] states is of no clinical significance.

It is obvious to us after a review of these cases that there is no characteristic gross appearance of carcinoma in situ of the cervix. Only eight of the 100 cases diagnosed by biopsy were regarded as suspicious clinically, and in none of the 35 cases found incidentally was the possibility of malignancy entertained preoperatively. Yet the majority of these patients were examined by two or more "early-cancer conscious" gynecologists. The diagnosis was established in 100 cases by routine biopsy (usually at 6 and 12 o'clock) of benign appearing cervical lesions. Thus, approximately 8,333 cervices were biopsied to detect those 100 cases of early cancer (1.2 per cent positive biopsies). With the current laboratory charge of $6.00 per case, it would cost $500.00 to find one easily curable cancer. This is a very reasonable price to pay.

Microscopic Appearance

The classification of the microscopic appearance of the squamous epithelium of the cervix in its various gradations from benign to malignant as used in this laboratory are as follows: 1. Basal cell hyperactivity or hyperplasia as described by Te Linde.[16] 2. Anaplasia in three degrees classified as "possible," "questionable," and "probable" carcinoma in situ. 3. Definite carcinoma in situ.

"Anaplasia of repair" is sometimes confused with noninvasive cancer. This type of anaplasia is characterized by increased mitotic activity, slight variation in nuclear chromatin content and size of the nuclei, but the basal nuclei are orderly, and the epithelium differentiates normally.

In "basal cell hyperactivity" the lower one-third or one-half of the epithelium is definitely anaplastic. There is no orderly arrangement of the basal nuclei. The nuclei of this anaplastic layer are hyperchromatic, variable in size and shape, and their long axes are disorderly. The nucleoli are large. The size of the nucleus is larger in relation to the cytoplasm than in normal or reparative epithelium. Mitoses are increased in number and are found anywhere in the involved epithelial layer, but their number is relatively unimportant. The failure to differentiate is the most important feature. The superficial one-half or two-thirds of the epithelium differentiates normally, but the basal portion looks malignant.

The three gradations of anaplasia (possible, questionable, and probable carcinoma in situ) are characterized by a more advanced form of basal cell hyperactivity involving the entire thickness of the epithelium except for a few layers of surface cells. The degree of anaplasia depends upon the amount of hyperchromatism and lack of differentiation. The gradation of the three stages is difficult to describe except by comparing one slide with another. Some just look more malignant than others.

Carcinoma in situ is completely undifferentiated squamous epithelium forming an intact layer of cells covering the portio vaginalis of the cervix, extending on occasion to the vagina but more frequently spreading upward into the cervical canal. In about 50 per cent of the cases it extends into the cervical glands. There usually is a sharp demarkation between the normal and malignant surface epithelium. On occasion there is an oblique line such as Schiller described although the transition between the malignant and benign epithelium may be gradual. Carcinoma in situ replaces the columnar cells of the endocervix or of the cervical glands as it advances. This is in contrast to the undergrowth which takes place in squamous metaplasia or epidermatization. The benign undergrowth of squamous metaplasia as distinguished from the total replacement of the endocervical epithelium by carcinoma in situ was first noted over twelve years ago, and no exception to the rule has been found to date.

Accuracy of Biopsy

How accurate are our biopsies in detecting these early and frequently small cervical carcinomas? The answer to this question involves too many variables to make it universally applicable. It requires the co-ordinated efforts of: 1. The clinician with his correct evaluation of the cervix and the Schiller test and his dexterous use of the biopsy punch; 2. The technician and her accuracy in embedding, cutting, and staining a small piece of tissue; and 3. The pathologist with his ability to recognize carcinoma in situ and lesser degrees of anaplasia which indicate repeated biopsies. The first biopsy in 13 of the 100 cases diagnosed by biopsy did not show definite carcinoma in situ (epidermoid hyperplasia, one; anaplasia, nine; and questionable or probable cancer in situ, three). In the thirteen cases the pathologist (P.A.Y., one; A.T.H., twelve) recommended a repeat biopsy which then showed the disease. This demonstrates the value of establishing the diagnosis before treating a diseased cervix and of secondary biopsies when the first shows anaplasia.

An analysis of fifty-four cases with two or more biopsies before hysterectomy shows the accuracy of cervical biopsy in this clinic (Table III). In two cases* only was the disease definitely more advanced than we anticipated.

In only one of the 135 cases was the disease confined to the limits of the cervical canal. This case is the only one in this series in which the vaginal

*Both cases are reported in detail under Microscopic Extent of Disease: S-45-233 and S-46-189.

smear gave the first clue to the possibility of malignancy. Positive Papanicolaou smears were obtained on three occasions at monthly intervals. The patient had no symptoms, and the first smear was taken merely as part of a routine examination at her request to exclude cancer. An office curettage of the cervical canal revealed cancer in situ. Then a dilatation and curettage was negative, and four cervical biopsies taken in the operating room under anesthesia failed to show cancer (none of the biopsies contained endocervical epithelium but just portio epithelium). Hysterectomy, performed two months after the negative dilatation and curettage, and three months afer the posiive office biopsy, revealed a carcinoma in situ of the cervical canal with gland involvement.

TABLE III. ACCURACY OF PREOPERATIVE BIOPSIES (2 OR MORE) IN 54 CASES OF HYSTERECTOMY

BIOPSY	NO. CASES	HYSTERECTOMY
Probable carcinoma in situ	3	Surface carcinoma in situ (2) Gland* involvement (1)
Surface carcinoma in situ	24	Chronic cervicitis (3) (cauterized preop.) Anaplasia (4) (cauterized preop.) Surface (10) Gland involvement (7)
Carcinoma in situ with gland and ? stromal invasion	27	Chronic cervicitis (radium) (1) (cauterized) (3) Anaplasia (cauterized) (1) Surface only (1) Gland and ? stroma (19) Definite early invasion (2)

*Surface carcinoma in situ with down growth into cervical glands.

Foote and Stewart[21] recently demonstrated that the lesion was inaccessible to the biopsy punch in two out of twenty-seven cases. Endocervical curettage is necessary for these rare cases. These authors also graphically demonstrated that routine biopsy at 6 and 12 o'clock would reveal the disease in only twenty out of twenty-seven cervices (74 per cent). Biopsies should not be done routinely at 6 and 12 o'clock. They must be taken as indicated by the Schiller test and they must contain the junction of the nonstaining squamous epithelium and the erosion. If the Schiller test is negative, then the erosion alone is all that is necessary to biopsy. In this clinic we consider any exposure of the glandular epithelium due to laceration of the cervix under the same category as an erosion, and these cases are biopsied routinely. A recent example verifying the value of this procedure is a mother of eight children whose cervix was cauterized post partum (without biopsy) two years before we saw her. The cervix was deeply lacerated, but due to cauterization only a very small area of "glandular" epithelium was visible. Biopsy of this area and the cervix, itself, after hysterectomy showed definite carcinoma in situ.

Microscopic Extent of Disease

The result of the microscopic study of the entire series is shown in Table IV, which lists the morphological variants or extent of the disease. In all cases there was surface involvement, but in 50.4 per cent the malignant epithelium was confined entirely to the surface. On the other hand, 20.7 per cent of the cases showed definite extension of the neoplastic epithelium into the glands entirely replacing on occasion the glandular epithelium. The authors

do not regard this glandular involvement as evidence of invasion which is contrary to the opinions of Te Linde, Novak, and Robert Meyer.[22] We thus concur with the opinions expressed by Ewing and Mallory in their previously quoted personal communications. Glandular involvement, therefore, merely indicates a more extensive replacement of the endocervical epithelium by carcinoma in situ.

TABLE IV. MICROSCOPIC EXTENT OF CARCINOMA IN SITU

	NO. OF CASES	PER CENT
Involvement of surface epithelium only	68	50.4
Involvement of glands	28	20.7
Glands and probable invasion of stroma	20	14.8
Probable or questionable early stromal invasion (alone)	12	8.9
Definite early stromal invasion (too early for frank cancer)	5	3.7
Carcinoma in situ pattern with definite cancer	2	1.5
Total	135	100.0

Thirty-seven cases (27.4 per cent) with or without glandular involvement exhibited questionable or minimal stromal invasion by the neoplastic epithelium. It was demonstrated in five of these thirty-seven cases after "step section" study of the entire cervix that such invasion was definite but early. Since a majority of pathologists would not accept these five cases in a group of true cancer patients, they are included in this series. Thus, they constitute a transitional group between true carcinoma in situ and carcinoma of the cervix. One of these five cases had leucoplakia and anaplasia of the cervix in September, 1943 (Fig. 6*A*). She refused treatment and was not seen again until October, 1945, two years and one month later. At this time a second biopsy was performed which showed a "probable carcinoma in situ" (S-45-2774). The cervix at hysterectomy, however, showed carcinoma in situ plus extension to the vagina and definite but early stromal invasion (Fig. 6*B*). Therefore, we feel that this case can be included in this series as one which was followed and observed to progress from anaplasia of the cervix in a leucoplakic area to carcinoma in situ and finally to an early invasive lesion. The remaining four of these five cases showed even less stromal invasion than the one illustrated.

The final two cases which are listed in Table IV as showing the carcinoma in situ pattern with definite invasion must be considered individually. One case (S-45-33) showed carcinoma in situ on the original biopsy. After the hysterectomy the cervix was cut into eight blocks. Four of the slides showed no tumor, two carcinoma in situ with glandular involvement, one only surface involvement, while the eighth slide showed definite early invasion. The second case (S-46-189) had two biopsies from an innocent appearing erosion on the posterior lip of the cervix. Both slides presented a typical picture of carcinoma in situ. Nine days later, at which time the vaginal smear was negative, three additional biopsies showed carcinoma in situ with gland involvement. Twenty-two days later a hysterectomy was performed. She was then fourteen days overdue, and pregnancy was probable. The vaginal smear taken that day was positive, and the hysterectomy specimen showed an early Grade II squamous cell carcinoma of the cervix and a normal pregnancy four weeks of age. These two cases are included in this series to demonstrate forcibly two important facts: 1. Typical carcinoma in situ must be regarded as a malignant disease of the cervix. 2. The absence of invasion in a cervix showing carcinoma in situ in one area can be demonstrated only by complete

serial block study of the entire cervix. While there is definite invasion, these two cases are so early that they are not included in the group of typical cancers of the cervix in this hospital (to be reported in the near future by Smith).

Ten cases are included in this series showing only the minimal criteria of carcinoma in situ, that is, marked basal cell activity with some degree of stratification. There are four additional cases, however, whose preoperative biopsies show only the minimal criteria, but the hysterectomy specimens show definite carcinoma in situ, one of which also had early invasion. The first biopsy in thirteen cases showed various degrees of anaplasia; yet, the second set of biopsies showed definite carcinoma in situ. One of these cases at hysterectomy showed early invasion.

In this series of cases eighty-three complete cervices were examined microscopically. The diagnosis of carcinoma in situ had been made preoperatively by biopsy in fifty-six of these cases, but the disease had been "cured" by the preoperative treatment in eleven (cauterization, ten, and irradiation, one). In five of the eleven "cured" cases anaplasia of the cervical epithelium was present showing a malignant tendency to persist.

Serial block, or step section, study was done on eighteen complete cervices as shown in Table V. Extension of the tumor from the cervix to the vagina was found in only one case in the entire series (Fig. 5*A* and *B*).*

TABLE V. STEP SECTION STUDY OF 18 EXCISED CERVICES

NO. OF CASES	BIOPSY	HYSTERECTOMY
8	Early invasion	Early invasion
4	Surface only	Surface only
2	Glandular involvement	Early invasion
1	Anaplasia—no tumor	Early invasion
3	Surface	No tumor*

*Cervix cauterized 11 days, 1 month, and 3 months before hysterectomy.

Vaginal Smear Correlation With Extent of Disease

Vaginal smears were studied in thirty-one cases with a 71 per cent degree of accuracy on the first or second smear and 61 per cent on the first smear alone. When these cases, however, were segregated as to the extent of the disease (Table VI), there was a 93 per cent degree of accuracy in the cases with gland or early stromal involvement and 53 per cent for cases with surface involvement only. The fact that carcinoma in situ of the cervix produces the same cytological picture in vaginal smears as cancer is just about the last bit of evidence needed to clinch the true nature of the disease, which has been doubted by so many pathologists for so long a time.

TABLE VI. RELATION OF VAGINAL SMEAR DIAGNOSIS TO EXTENT OF DISEASE IN 31 CASES

EXTENT OF CARCINOMA IN SITU	VAGINAL SMEAR			
	CORRECT		FALSE	
Surface involvement only	9	53 per cent	8	47 per cent
Surface involvement plus glands and stroma	13	93 per cent	1	7 per cent
Total	22		9	

*Since this study was concluded, two additional cases of extension to the vagina have been observed. In both cases the Schiller test delineated the malignant vaginal epithelium. In one of these cases a radical panhysterectomy with en bloc pelvic node resection was performed removing two-thirds of the vagina as well. Twenty-four lymph nodes were negative.

Results of Cauterization of the Cervix

In the early days of this study, five to ten years ago, the rule to biopsy and have a pathological diagnosis before treating an "eroded" cervix was not followed strictly as it is at the present time. Thus, the great majority of the forty-three cases treated originally by cauterization were cauterized at the time of the original set of biopsies. Only one was cauterized deliberately after the diagnosis had been established.

Sixteen of the forty-three cases were treated five to twelve years ago, and all are alive and free of disease at the present time, but four of the sixteen were not cured by cauterization. These four cases, in whom the disease persisted after cauterization as shown by biopsy, were treated by hysterectomy or radium one, one and one-half, eight, and fourteen months later and are free of disease, nine, eight and one-half, eleven, and five years postoperative. Of the twelve cured cases two had a hysterectomy three and four months after cauterization for "cancer hysteria," a third for functional flowing six years later, and no cancer was found in their cervices. Nine of the twelve cured cases have had no further treatment except repeat biopsies and vaginal smears which have been negative.

Twenty-seven of the forty-three cauterized cases have been followed less than five years (sixteen months up to four and one-half years), but the authors feel reasonably certain of the final results for the entire group of forty-three because of the careful follow-up study by smears and biopsies. To date, of the forty-three cauterized cases, eighteen have had a hysterectomy, two have been treated with radium, and twenty-three have had no other treatment. In six of these eighteen hysterectomy specimens there was no cancer.

The study of the forty-three cases originally treated by cauterization gives us a definite working plan to follow in advising treatment for each individual case. This plan is the result of comparing the end results with the microscopic extent of the carcinoma in situ. Thus, 85 per cent of twenty-seven cases (Table VII) have been cured when the disease was localized to "surface involvement only," whereas, only 37 per cent of sixteen cases were cured when the disease had spread to the cervical glands with or without minimal stromal invasion. If multiple biopsies and endocervical curettage show no gladular involvement and there is a desire to preserve reproductive function, that patient may be offered cauterization with an apparent 85 per cent chance of cure. If the treatment fails to cure the disease as determined by biopsies two to six months later, her life has not been jeopardized by the delay while attempting conservative therapy. On the other hand, if the cervical glands *are* involved or there is early or even questionable stromal invasion, conservative therapy (cauterization or sharp conization) may be offered although it is not likely to produce a cure. The delay of two or three months, however, will not jeopardize the patient.

TABLE VII. EXTENT OF DISEASE IN RELATION TO RESULTS FROM CAUTERIZATION OF CERVIX (43 CASES)

EXTENT OF CARCINOMA IN SITU	APPARENTLY CURED		NOT CURED	
Surface involvement only	23	85 per cent	4	15 per cent
Surface involvement plus glands and stroma	6	37 per cent	10	63 per cent
Total	29*		14†	

*Determined by subsequent biopsies and vaginal smears (23) or hysterectomy (6).
†Determined by subsequent biopsy; 2 treated with radium, 13 by hysterectomy.

A complete hysterectomy was performed or radium applied within three months on eleven of the fourteen cases not cured by cauterization (Table VII). The other three cases were followed without further treatment for fourteen,

eight, and six months, respectively, before radical therapy; hysterectomy in two cases and irradiation in the third, and they are alive and well five, eleven, and two years later.

Pregnancy After Cauterization for Carcinoma in Situ of Cervix

Six patients have become pregnant among the group of twenty-nine cases (Table VII) who apparently have been cured by cauterization of the cervix; four had normal living children, one miscarried, and one patient had a three months' gestation as of April 1, 1949. One patient was pregnant a second time and was due to deliver in August, 1949. One of the above four women who have had normal living children has since had a hysterectomy for a pseudomucinous cystadenoma of the ovary. Her cervix showed no disease.

The miscarriage occurred in a 31-year-old patient who sought advice because of leucorrhea for many years and postcoital bleeding and sterility since her marriage one year before. There was a positive Schiller test around the periphery of a wide congenital erosion. Biopsies at 1 and 5 o'clock showed chronic cervicitis with squamous metaplasia and anaplasia. One month later biopsies at 1, 7, and 10 o'clock showed carcinoma in situ with benign epidermatization of the glands. The vaginal smear at this time was positive. The condition was explained to the patient and her husband, and they preferred conservative treatment in the hope that they might have children. Three more biopsies were taken, all showing carcinoma in situ. The cervix was thoroughly coagulated in the Out-Patient Department, and two months later the vaginal smear and biopsy were negative. One year later (October, 1947) she was admitted to the hospital because of an incomplete spontaneous abortion. At the time of the curettage a cervical biopsy was taken which showed chronic cervicitis with squamous metaplasia. She is still under observation and will be followed indefinitely. This is the only patient deliberately treated by cauterization.

Still another patient, a mother of two children, had a repair of a large cystocele and rectocele at the age of 22 years. An erosion of the cervix was biopsied and cauterized at the same time. The biopsy showed invasive cancer, early, but too definitely invasive to include in this series. One year later her cervix was normal by biopsy and Schiller test. Then she became pregnant. A biopsy at three months was negative, but she had an induced abortion and died of septicemia in a hospital in a neighboring state. Autopsy showed no cancer. Apparently she had been cured of cancer by cauterization.

The experience with these cases shows that it is possible to preserve reproductive function in young women and safe for them to have children if there is no evidence of invasion or persistence of the disease after cauterization and repeated biopsies. However, if repeated biopsies show that the disease is still present and there is gland or early stromal involvement, it is dangerous to attempt conservative therapy.

Treatment and Results

Table VIII shows the final treatment for the entire series thus far including the four trachelorrhaphy patients whose original diagnosis of carcinoma in situ was missed. They were subsequently treated by irradiation for clinical cancer. Six patients had radium and x-ray therapy in addition to complete hysterectomy. Irradiation after vaginal or abdominal total hysterectomy is considered unnecessary at the present time. Amputation of the cervix was performed on six patients, two of whom had postoperative irradiation, which is necessary if the extirpated cervix shows incomplete removal of the disease. At the persent time, however, it is felt that hysterectomy is preferable for these cases.

TABLE VIII. ULTIMATE TREATMENT OF ENTIRE SERIES

TREATMENT	NO. OF CASES	DEATHS		
		CANCER OF CERVIX	OTHER CAUSES	FROM TREATMENT
Complete hysterectomy (69) Complete hysterectomy plus radium and x-ray (6)	75		1	
Amputation of cervix (4) Amputation of cervix plus irradiation (2)	6		1	
Vaginal hysterectomy	2			
Supravaginal hysterectomy plus radium	3	1		
Radium	12		3	
Radium and x-ray	4			2
Cauterization and x-ray	1			
Cauterization of cervix	23			
Trachelorrhaphy*	4	3		
Polypectomy	1			
No treatment	4			
Total	135	4	5	2

*Original diagnosis missed. All developed invasive cancer 3½ to 6½ years later and then were treated. Only one survivor.

In twenty patients the disease was treated primarily by irradiation; supravaginal hysterectomy followed by radium, three cases; radium alone, twelve cases; radium and x-ray, four cases; and cauterization and x-ray, one case. Six of these patients are now dead; one from cancer of the cervix; two from irradiation complications; and three from other causes—pulmonary tuberculosis, heart disease, and cancer of the breast.

The above death from carcinoma of the cervix was a 30-year-old patient treated in 1929. Biopsy (one specimen) of the cervix and cauterization were done at the time of a supravaginal hysterectomy for fibroids and endometriosis. The first sections of the cervix were suspicious, but additional sections showed definite carcinoma which we now interpret as carcinoma in situ involving the glands. However, in 1929, another pathologist said, "Probably not malignant." A single application of radium (4,800 mg. hr.) was given one month postoperative at which time the cervical stump was described as well-healed and the pelvis negative. Three years later she was treated at the Pondville State Hospital for an "extensive recurrence" and died five and one-half years after the original treatment.* Invasive cancer must have been present elsewhere in her cervix, but the biopsy specimen showed only the "surface coating" nearby.

The first death attributable to treatment per se occurred in July, 1944, in a patient treated in December, 1943. A biopsy showed carcinoma in situ involving the glands was taken at the time of a repair operation and cauterization of the cervix. From then on everything concerning her treatment can be criticized. Two weeks later, without another biopsy, she was given 3,200 mg. hr. of radium followed by x-ray therapy (4,800 r.u.). Thirty-five days after the one and only biopsy, the second dose of radium (4,000 mg. hr.) was applied. Death occurred eight months after treatment of pelvic abscess and intestinal obstruction attributable to irradiation.

The second death associated with treatment also occurred in 1944. One of three cervical polypi was removed in the Out-Patient Department and showed carcinoma in situ involving the glands. The patient was admitted to the hospital, and 3,000 mg. hr. of radium was applied to the cervical canal. The

*Reported by Smith and Pemberton in 1934.

other two polypi and a cervical biopsy removed at the time of radium treatment showed no cancer. In spite of these negative findings, she received x-ray therapy (6,000 r.u.) as an ambulatory patient, and died of diabetic coma two days after the last x-ray treatment. It seems fair to assume that x-ray sickness precipitated the diabetic complication because she had been able to control her diabetes easily for several years. Here again, as in the previous case, it is suspected that the pathologist's report was not read in detail.

Table IX lists the type of treatment and results in detail of sixty-nine patients in this series who were treated before February, 1944. All except two have been followed and examined for from five to sixteen years (excluding four who died under five years). Two of the hysterectomized patients have not been followed beyond three months and one year, respectively, because they are untraceable.

TABLE IX. TREATMENT AND RESULTS FIVE OR MORE YEARS POSTOPERATIVE (69 CASES)

Trachelorrhaphy (mistake in original diagnosis)	4 cases
3 died of cancer of the cervix 4 years, 3 months; 6 years, 7 months; and 8 years, 3 months.	
1 treated with radium 4 years, 8 months postoperative for cancer of the cervix. Alive and well 16 years.	
Excision of cervical polyp	1 case
Alive and well 12 years, 8 months postoperative.	
Radium with or without x-ray	18 cases
1 case, recurrence 3 years postoperative. Died of cancer of the cervix 5 years, 6 months postoperative.	
1 case died 1 year postoperative of irradiation complications.	
1 case died 2 years postoperative of pulmonary tuberculosis.	
15 cases alive and free of disease 5 to 15 years postoperative.	
1 case died of heart disease 5 years, 9 months postoperative.	
1 case died 7 years, 7 months postoperative of cancer of the breast (2 years postoperative).	
Amputation of cervix	3 cases
1 case, age 75 years, died 3 years, 9 months postoperative of heart disease.	
2* alive and well 9 and 11* years postoperative.	
Cauterization of cervix (all alive and well 5 to 12 years postoperative)	16 cases
4 cases not cured.	
1 case, radium 8 months later. Alive and well 11 years postoperative.	
1 case, radium 6 weeks later. Alive and well 8 years, 6 months postoperative.	
2 cases complete hysterectomies 1 month and 14 months postcautery. Alive and well 9 and 5 years postoperative.	
12 cured: Alive and well 5 to 12 years postoperative	
9 no further treatment except biopsies and smears.	
3 hysterectomies 3 months, 4 months, and 6 years postcauterization—no cancer.	
Complete hysterectomy	27 cases
24 alive and well 5 to 15 years postoperative.	
1 died of cancer of endometrium 5 years postoperative (autopsy).	
2 cases alive and well 3 months and 1 year (not followed).	

*One case, a deliberate experiment, followed 1 year after diagnosis was made, and definite invasive cancer of the cervix found in amputated cervix.

The follow-up studies on the more recent cases in this series in the past five years amply justify the finely separated histological classification used in this laboratory for the suspicious lesions and early malignancies of the cervix. By repeated biopsies, we have observed basal cell activity apparently progress to anaplasia and possible or even questionable carcinoma in situ. Basal cell activity, anaplasia, and definite carcinoma in situ may be seen in one cervix.

In July, 1943, a biopsy (S-43-1109) showed a very disturbing anaplasia of the cervix. The patient did not keep her appointment, and we did not see her again until February, 1946, when she had advanced cancer of the cervix and died in June, 1947. She had been treated elsewhere in July, 1945, two years after the biopsy. Because of lack of data this case is not included in the series although other cases (Nos. 83, 86, and 119) have shown apparent progression from probable carcinoma in situ to the definite disease with involvement of the glands in from two months to eleven months.

A study of the end results in relation to the type of treatment at the time or within two months of original diagnosis, gives us the most valuable information. Twelve cases received no treatment or inadequate treatment, five of whom developed invasive cancer eleven months to six and one-half years later; in two additional patients the disease persisted as shown by hysterectomy six and eleven months later; in four others* it regressed, and in the final one the disease was cured by the removal of a cervical polyp (Table X).

TABLE X. END RESULT IN RELATION TO TYPE OF TREATMENT AT TIME OF ORIGINAL DIAGNOSIS

TREATMENT	NO. OF CASES	DEVELOPED INVASIVE CANCER	CARCINOMA IN SITU PERSISTED	CARCINOMA IN SITU CURED BY CAUTERY	CARCINOMA IN SITU REGRESSED AFTER BIOPSY
Adequate[a]	80	1[c]	0	0	0
Inadequate[b]	5	4[d]	0	0	0
None except biopsies	7	1[e]	2[f]	0	4[h]
Cauterization	43	0	14[g]	29	0
Total	135	6	16	29	4

a. Complete hysterectomy; amputation of cervix with or without irradiation; or irradiation alone.

b. Trachelorrhaphy 4 cases; Excision of cervical polyp 1 case—alive and well 12 years, 8 months.

c. 4800 mg. hr. radium 1 month after biopsy. Died of cancer of cervix 5½ years later.

d. Invasive cancer recognized 3½ to 6½ years later, treated with radium—1 survivor. Original diagnosis missed.

e. Deliberate experiment: developed invasive cancer 11 months later (alive 11 years postoperative).

f. Two cases had hysterectomy 6 and 11 months later.

g. Carcinoma in situ persisted as shown by biopsy or hysterectomy 2 weeks to 14 months later.

h. Carcinoma in situ regressed to anaplasia after second or third biopsy—2 cases followed through pregnancy.

One of the above untreated cases had negative vaginal smears and anaplasia of the cervix on two successive biopsies. She then became pregnant. In the second month a biopsy showed carcinoma in situ in one out of eight sections made from one biopsy, and the vaginal smears became positive and remained positive until the sixth month. During this time the innocent erosion became suspicious, and the Schiller test, previously negative, became positive. She had a normal delivery, her fifth, at full term. Six weeks post partum the cervix was practically normal, and the Schiller test and vaginal smear were negative. Anaplasia of the type we have seen progress to carcinoma in situ, however, still persists. She is now pregnant again.

Comment

All of the evidence obtainable from this study and from the experience of such careful workers as Schiller, Te Linde, and Pund and Auerbach, point to the validity of the eventual clinically malignant behavior of carcinoma in situ

*All four cases had positive vaginal smears, but their biopsies showed only the minimal criteria, i.e., surface differentiation. At this stage the disease may be reversible.

of the cervix. Cases have been observed to progress from "marked basal cell hyperactivity" to anaplasia and eventually to definite carcinoma in situ. Anaplasia of the squamous epithelium of cervix has been observed in this series to progress to early invasive cancer. In one deliberate and five unintentional clinical experiments carcinoma in situ has been seen to progress to invasive cancer in from eleven months to over six years.

The fact that this disease has been found to occur at a constant rate of approximately 1.2 per cent in routine biopsies of diseased but clinically benign cervices during a period of ten years proves that it is a disease entity which occurs at a regularly predictable rate. Since it occurred in women whose average age is about nine years less than that for frankly invasive and clinically obvious cancer of the cervix, its long latent period is evident. It is a well-known fact that some cancers progress faster than others, and so it is with carcinoma in situ of the cervix. To this present day we do not regret or fear studying a case up to one year before deciding upon the type of treatment. It must be emphasized, however, that the evaluation of a case must be done by frequent and multiple biopsies aided by the Schiller test as well as endocervical curettage.

In these cases the chief responsibility rests upon the accurate interpretation of the cellular morphology of the biopsy specimen by the pathologist. On the other hand, the careful selection of the biopsy site by the clinician and his dexterity in performing the biopsy so as to include, undamaged, the exact area intended are of equal importance. Occasionally the pathologist will report "portio epithelium only" or "endocervical epithelium only." These reports mean inadequate or improperly performed biopsies because the junction of the two cervical epithelia should be present in a perfect biopsy since most cancers begin at that junction.

Not infrequently slides are sent to this laboratory for an opinion after a diagnosis of carcinoma of the cervix has been made elsewhere. Some of these "consultation cases" are just carcinoma in situ with or without gland involvement. Radical treatment such as Wertheim hysterectomy or a full course of irradiation is, therefore, not justified unless further study reveals truly invasive cancer. Also, cervices showing epidermatization or squamous metaplasia are confused with invasive cancer or carcinoma in situ with gland involvement. Treatment of any case should not be done until the disease is evaluated by at least a second set of biopsies and endocervical biopsy or curettage. All of us have made these mistakes, but with more experience they become less frequent.

The hysterical fear frequently aroused by the diagnosis of carcinoma in situ is without reason. There is no need to perform a hysterectomy immediately, or the next week, or the next month after the first biopsy. The case should be evaluated carefully first especially because this is a disease of younger women, many of whom want a child or more children (41.1 per cent under 35 years of age and 17.0 per cent under 30). When the disease is early (surface involvement only) cauterization or sharp shallow conization can be offered as a nonsterilizing treatment to these young women with an 85 per cent apparent chance of success. In this series eight patients have become pregnant of whom six have normal living children, one is normally pregnant at three months' gestation, and the eighth had a miscarriage. Pregnancy occurred in six of the eight patients after successful conservative treatment and in two in whom the disease either regressed or was cured by biopsy.

The problem of establishing the diagnosis of this early form of cervical cancer on a nationwide basis is a difficult one. Not many physicians have the time, equipment, or ability to perform selective cervical biopsies of all eroded

or positive Schiller test cervices as are done in this clinic. Nor are cervical biopsies very accurate in any clinic not highly specialized in this art as demonstrated by Fremont-Smith, Graham, and Meigs[23] at the Massachusetts General Hospital. They found in a general hospital that vaginal smears were far more accurate than biopsies which is exactly opposite to our findings. Vaginal smears, however, are reliable when the in situ cancer is more advanced, i.e., with gland involvement. Here again, very few physicians have at their disposal a reliable laboratory for the reading of vaginal smears so it is rather obvious that the majority of women cannot be given, at the present time, the advantage of early diagnosis by either biopsy or vaginal smear.

What then can be done to diagnose early cancer of the cervix while it is in the easily curable "in situ" stage? First of all, basal cell hyperactivity or anaplasia and carcinoma in situ have been found in this clinic at the periphery in many congenital erosions as well as in the post-partum erosions or exposed endocervix in lacerated cervices. If these cases are not suspicious clinically, have no abnormal bleeding, and the Schiller test is negative, thorough cauterization without biopsy should be done. Such a cauterized cervix, after one adequate cauterization, should be restored to a normal appearing cervix inside of two to three months. By a "normal appearing cervix" it is meant that all of the erosion has been replaced by squamous epithelium which stains with Gram's iodine solution. If carcinoma in situ persists after cauterization, the Schiller test will be positive and/or some "erosion" still will be present. In these cases biopsy is mandatory.

With respect to the value of the Schiller test in this series, twenty-seven out of twenty-nine cases so tested had a positive test (93 per cent). More extensive application of the test in the past two years has verified this fact. Therefore, biopsy of all cervices with nonstaining squamous epithelium should be mandatory in spite of the fact that over 90 per cent of positive Schiller test cervices show only paraleucokeratoses or other benign lesions. A physician cannot assure his patient that she does not have cancer of the cervix if there is an erosion or a positive Schiller test unless he has ruled it out by biopsy.

To prove that carcinoma in situ of the cervix may spontaneously regress is difficult because it is theoretically possible to remove the entire lesion in one biopsy. This apparently has been recently demonstrated in a cervix removed by hysterectomy a few days after the biopsy. In this series, however, there are four untreated cases in whom no cancer can be found by vaginal smear or biopsy one and one-half to two years after the original positive biopsy and definitely positive vaginal smears. A re-evaluation of the original slides in these four cases shows that all exhibit some surface differentiation which may represent the reversible stage of the disease. Their apparent regression, on the other hand, may mean that the entire lesion was removed. Whether these four cases have regressed or were cured by biopsy demonstrates the extreme importance of a calm and deliberate appraisal of all of these lesions before embarking upon radical treatment.

The careful and accurate study in cases of young women with child-bearing aspirations has been discussed. When the disease is found in women in the older age groups or in those patients, young or old, who have some other condition indicating a hysterectomy, it is just as essential to evaluate the extent of the disease. Invasive cancer must be ruled out before a simple total hysterectomy, with or without preservation of ovarian function, can be considered safe and the proper treatment. Because of the long follow-up on the twenty-four hysterectomized patients treated before 1944 (five to fifteen years) and because of the negative lymph nodes in three recent Wertheim hysterectomy cases, a routine total hysterectomy plus one centimeter of

vaginal cuff is considered adequate treatment. The Schiller test helps to decide how much vaginal cuff should be removed. The authors do not feel that a Wertheim hysterectomy is necessary, or even TeLinde's modified Wertheim operation, if the cases are studied adequately before treatment. Irradiation therapy, although it will cure the disease, should be reserved for the rare poor-risk patient. No patient in this clinic has been treated by irradiation for carcinoma in situ since 1944, and the last two so treated are deeply regretted because they are the only fatalities due to treatment in this series.

Summary and Conclusions

1. Six cases of carcinoma in situ of the cervix have been observed in this clinic to progress to invasive cervical cancer in from eleven months to six and one-half years. Three of these patients died of their cancer whereas three are living and well four, eleven, and sixteen years after treatment for the invasive carcinoma. One of the latter patients while under direct observation developed invasive carcinoma at the original biopsy site during a period of eleven months.

2. One case of "marked anaplasia" of the cervix was found to have cancer of the cervix two years later and died of cervical cancer two years after treatment. It is suspected that the original biopsy showing anaplasia was taken from the periphery of an invasive cancer although this was not suspected clinically.

3. "Basal hyperactivity," anaplasia, atypical or equivocal carcinoma in situ and definite carcinoma in situ may be found either together, separately, or in a cervix with obvious cancer. Although it is impossible to prove, cases have been observed which have seemed to progress through these stages of anaplasia and finally become carcinoma in situ.

4. Carcinoma in situ of the squamous epithelium of the cervix represents either malignancy in its early stage or noninvasive cancer at the periphery of an infiltrating lesion. Therefore, when it is found, invasive carcinoma must be ruled out by multiple biopsies or serial block study of the entire surface of the cervix.

5. If no invasion is found on the first or second biopsies, a deliberate study of the cervix may be done by repeated multiple biopsies and vaginal smears for at least six months with no risk to the patient. If the carcinoma in situ involves only the surface epithelium and does not involve the cervical glands, thorough destruction of the surface lesion by cauterization or complete excision by sharp conization will apparently cure 85 per cent such cases. Reproductive function, thus, may be preserved in young women. Those not cured by these conservative methods should have a simple total hysterectomy removing as much vagina as is indicated by the Schiller test. Removal of the ovaries is not necessary.

6. If after thorough study the carcinoma in situ is found to involve the cervical glands but there is no stromal invasion, a simple total hysterectomy is indicated.

7. At present all available evidence indicates that lymphatic spread does not occur from carcinoma in situ of the cervix. Therefore, pelvic lymph node dissection is not indicated in cases adequately studied before treatment is undertaken. A simple total hysterectomy for carcinoma in situ after only *one* biopsy is hazardous because invasive cancer has not been ruled out preoperatively.

8. Adequate evaluation and study of most of these cases can be done without hospitalization by the use of a good biopsy punch and an accurately interpreted Schiller test. Endocervical curettage, submitting blood clot as well as tissue, is an essential part of the study of each case.

9. A normal cervix is one completely covered with squamous epithelium which stains dark brown after applying Gram's iodine solution. No glandular epithelium should be visible except that inside the cervical canal. All others are regarded as abnormal and all erosions, lacerations with eversion, "spotty erosions" on hypertrophied cervices and positive Schiller test areas should be biopsied. Carcinoma in situ is found in 1.2 per cent of such routine biopsies.

10. Only 6 per cent of the cases in this series had suspicious cervices and 46 per cent were asymptomatic. Abnormal bleeding occurred in only 30 per cent of the cases.

11. Eight of fifteen cases who had never been pregnant had what appeared to be innocent congenital erosions.

12. The average age of women with carcinoma in situ of the cervix is 38 years, 41 per cent being under the age of 35 years and 17 per cent under thirty years.

13. Vaginal smears are reasonably accurate (93 per cent) when carcinoma in situ involves the cervical glands but will reveal only 53 per cent of those showing just surface involvement.

14. Pregnancy is not hazardous after curing carcinoma in situ of the cervix by cauterization. Six such patients in this series have become pregnant, four having had normal deliveries, one miscarried at three months, and the sixth is at present three months pregnant. Two untreated cases, whose disease has regressed or was cured by biopsy, have subsequently had normal children.

15. Five-year follow-up study on sixty-nine patients with cervical carcinoma in situ shows that none with adequate study before treatment has had a recurrence or died of the disease.

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Discussion

DR. GEORGE H. GARDNER, Chicago, Ill.—Probably we are still confused regarding certain aspects of this condition, but must agree that this portrayal of twenty-three years' experience at the Free Hospital helps to clarify some of the issues.

Carcinoma in situ was found in 1.2 per cent of their cervical biopsies taken routinely from every clinic patient with either an eroded, an everted, or a positive Schiller test cervix. The authors accept the incidence of invasive cancer of the cervix as 1.6 per cent, and, without further ado, assume that carcinoma in situ occurs at a regular predictable rate comparable to the incidence of invasive cervical cancer.

Next, the average age of their carcinomas in situ is 38.7 years; with TeLinde it was 37.1 years. Both groups consider it highly significant that there is a lag of about ten years between the average of in situ lesions and the average age of invasive cervical cancers.

The Boston group continues with additional data which suggest that carcinoma in situ may be an irreversible process; for example, they observed six carcinomas in situ which, within eleven months to six and one-half years, progressed to invasive cancer. Another patient originally showed only "marked anaplasia" but progressed to invasive cancer within two years and died of her cancer two years later. They have also found basal cell hyperactivity, anaplasia, atypical carcinoma in situ as well as definite in situ cancer, not only separately and together, but also in a cervix with obvious cancer. All of this suggests but fails to prove that carcinoma in situ is irreversible.

They are enthusiastic about the Schiller test as an aid in accurate delineation of surface lesions and for determination of the exact sites to be biopsied. They do not share Meigs' confidence in vaginal smears but they are ardent advocates of repeated biopsies, and I agree that every original diagnosis must be confirmed. However, I doubt the effectiveness of biopsies in determining the extent of the disease and the degree of invasion, and I suspect a lack of agreement among the authors on this point since their paper contains conflicting statements; for example, "the absence of invasion in a cervix showing carcinoma in situ in one area can be demonstrated only by complete serial block study of the entire cervix." With this I agree most heartily, but find difficulty in accepting the following: "If multiple biopsies and endocervical curettage show no glandular involvement, and there is a desire to preserve the reproductive function, that patient may be offered cauterization with at least a 75 per cent chance of cure." To go further, they may be justified in rejecting extension of surface cancer into cervical glands as evidence of invasion. But when one is seeking order out of chaos it is regrettable that they further complicate an already confused subject by introducing a rather complex histopathological classification for these lesions. Actually they suggest anaplasia as the name for those intermediate cases which are more extensive than basal cell hyperactivity but do not show involvement of all layers of the squamous epithelium, their definition of true carcinoma in situ.

If we are agreed that carcinoma in situ is cancer, then we are also agreed that effective treatment must eradicate the cancer. However, experience to date strongly suggests that it need not be so radical as for invasive cancer. Consequently total hysterectomy with removal of an adequate vaginal cuff seems to be satisfactory. Treatment of carcinoma in situ by cauterization alone was an interesting experiment but should not be continued irrespective of how efficient the subsequent follow-up may be. Furthermore, I cannot accept either trachelorrhaphy or conization alone as adequate treatment. And now that the Free Hospital has survived twenty years of therapeutic experimentation, I hope they will do more total hysterectomies for carcinoma in situ, a highly desirable policy since it would yield; (1) Better specimens for study; (2) adequate material to determine the extent of the disease and the degree of invasion, if any; (3) more evidence to justify anaplasia as a type of carcinoma in situ and to clarify its suggested subdivisions, and (4) last but not least, a larger series of cured patients.

DR. ARTHUR HERTIG, Boston, Mass.—We are trying to be rigid in our morphological criteria in diagnosing cervical carcinoma in situ. The situation is somewhat confused by differences of opinion regarding these morphological criteria of preinvasive cervical malignancy and furthermore by differences in terminology among those investigators who actually recognize that such a biological entity exists. One should, therefore, be careful to distinguish between such a terminological and biological argument.

Admittedly there are an insufficient number of cases which have been followed through the various stages of squamous cervical malignancy from anaplasia, surface carcinoma in situ, and subsequent glandular involvement to stromal invasion and true clinical carcinoma.

We have tried to give evidence that some of these anaplasias ultimately develop into carcinoma in situ or actual invasive carcinoma. We have not included in this series any cases in which anaplasia was the only diagnosis without further evidence of subsequently developing carcinoma in situ. Dr. Younge showed you merely one classic example. He could have shown others.

There are several variants of squamous carcinoma of the cervix and I am not always able to figure out which particular carcinoma in situ will go on to any given definitive squamous malignancy. The average Grade II type probably arises on the basis of the classic case Dr. Younge showed you since most of the carcinomas in situ are of that variety.

We do not believe that gland involvement constitutes true invasion because the morphologically malignant tissue is still within epithelial structures. Admittedly this is a later stage of carcinoma in situ but there is no stromal invasion since the basement membrane is still intact.

It should be emphasized that we do not believe that cauterization is the proper or even usual method of treating these patients. This study covers approximately twenty years and early in this period cauterization was done at the time the biopsy was taken. Such a case was, therefore, unsuitable for the study of the genesis of cervical malignancy. I think that cauterization is justified in the occasional case requiring conservation of reproductive function providing the surface epithelium is the only structure involved, the patient is young, the situation is explained to her and she desires to take the chance. These are individual matters which should be settled between physician and patient. In the deliberately cauterized cases which Dr. Young presented, the four patients who subsequently had living babies seems to justify that point of view.

DR. HARVEY B. MATTHEWS, Brooklyn, N. Y.—I have a question and I seek the answer from someone in this audience. The cytological problem and the biopsy have been given full evaluation but absolutely nothing has been said about the psychological problem in relation to the woman who has to be told that she has cancer. Dr. Younge showed data of a young woman who had had no symptoms referable to her pelvis but in the course of a routine physical examination vaginal cytology was done and "lo and behold" cancer in situ of the cervix was found. Finally hysterectomy was recommended. Imagine the shock

to the patient and her family. Now, just how does Dr. Younge or anyone else break such information to the patient? This is a serious matter to these women and cannot be "laughed off." I feel sure that there are others here who would like the answer to my question.

DR. ARTHUR HERTIG.—I suggest that Dr. Younge, who is a good psychologist in regard to this problem of breaking the news to the patient, answer Dr. Matthews' question. Dr. Younge gets his patients to come back month after month, and moreover does not scare them to death when he tells them what the situation is in respect to the suspicious lesion.

DR. ISIDOR C. RUBIN, New York, N. Y.—At the beginning of my career I had the good fortune to study at the laboratory of Schottlaender under Von Rosthorn. The now famous book of Schottlaender and Kermauner on carcinoma of the uterus was published in 1912. It is a classic and as useful today as it was when published.

There were two schools of thought then as there are today. Schottlaender predicated that the epithelium of the vaginal portio underwent certain changes with atypicalism of the cells which he described as "unrest," all of which were beautifully illustrated by a number of the slides shown this morning. There was another school which claimed that these proliferative changes are due to some unknown stimulus not necessarily precancerous in nature. Further that we cannot speak about cancer lesions unless there is positive lymphatic invasion. Now we have carcinoma in situ which has been referred to by some as epithelioma of the cervix similar to basal epithelioma of the skin.

The question is, what to do when you come upon a smear which is positive? I had one patient upon whom I did a trachelorrhaphy and the report was carcinoma in situ. She refused further operation or treatment of any kind. According to her husband, she already had carcinophobia. I saw her the other day, eleven or twelve years older, and the cervix is just as good as it was then and the vaginal smear was negative. Incidentally, she had had about 14,000,000 units of female sex hormone over a period of eight or nine years which should have added theoretically to the cancer stimulation but did not. I believe a case like this, if at all possible, should be followed regularly as Dr. Younge has followed his. From my point of view, I would prefer to see these patients submit to operation when there are outspoken signs of cell atypicalism characteristic of early carcinoma.

DR. OTTO SCHWARZ, St. Louis, Mo.—I want to recall a paper read by Dr. Robert Crossen at the last meeting of the Society. He and his father have been doing routine conizations for benign lesions of the cervix. I feel that in cases of benign lesions of the cervix conization is indicated; microscopic sectioning will rule out any carcinoma and you can detect lesions such as have been discussed. When such lesions occur, you have done no harm and you have put the patient in a position where you can watch her or treat her further. At first glance this may seem radical but I feel very definitely that the procedure is prophylactic; you do no harm and the patient is made more complacent.

DR. W. G. COSBIE, Toronto, Can. (by invitation).—In the realm of cancer therapy at the present time, the most important factor is early diagnosis and when we are faced with the fact that present methods of treatment are reaching a plateau above which they seldom rise, it is natural that every effort should be made to obtain a diagnosis even before invasion has taken place. One hears much of the value of cancer prevention or detection clinics. In Ontario we have made a survey recently because we realized that the people who are coming to these clinics are nearly all from the better economic brackets. We found that to extend such a service to the whole province would cost about $39,000,000 a year. We wonder if there are not better ways of spending the money which we have available for the diagnosis and treatment of cancer than in the widespread establishment of such clinics.

There is another phase of this question which is worthy of consideration. The vaginal smear has received such wide publication that not only patients but general prac-

titioners are asking if a smear cannot be taken to the exclusion of the idea that the basic and first step in the diagnosis of carcinoma is a proper examination of the patient. One is always impressed by the fact that in any series of cases where smear diagnosis is successful there are included a large number of patients in whom the tumor would have been recognized with ease had a routine pelvic examination been made.

There is another problem opened by a paper such as this on carcinoma in situ. Our experience has been that there is a great difference of opinion between pathologists as to whether the condition is present in any particular case. The findings of smear or biopsy are open to such a variety of interpretations. I think that Dr. Novak presented the most important feature of this difference of opinion when he drew attention to the fact that what has been called glandular invasion may be nothing more than metaplasia in relation to the cervical gland epithelium.

There is also the question as to what we are going to do with the patient when the diagnosis of carcinoma in situ has been made. It seems to me that total hysterectomy alone will allow the examination of sufficient tissue to determine the true significance of the condition. It is altogether likely, however, that time will prove that this procedure is not justifiable as the basis of proper treatment.

DR. YOUNGE (Closing).—Apparently I gave the wrong impression about our attitude toward the vaginal smear. I had hoped to make it clear that smears are 93 per cent accurate when carcinoma in situ becomes a lesion which is potentially dangerous, that is, with involvement of the cervical glands. We do use the vaginal smear and we do depend upon it.

In answer to the remark about serial block study of the entire cervix being necessary to rule out invasion, we have had in this group of cases eighty-three complete cervices to study. In only two of these cases did we miss the diagnosis preoperatively of early invasion. Yet, the lesions were so small that a simple total hysterectomy was sufficient treatment. We know of a fair number of patients (at least thirty) who by mistake have had total hysterectomy without a suspicion of carcinoma being present. After the hysterectomy early invasive cancer was found; yet those patients are among the best follow-up results obtained by surgical treatment. Some may disagree with that statement, but I believe Dr. Meigs will back me up.

We do not really advocate cauterization of the cervix as the treatment for carcinoma in situ. Only one case was cauterized deliberately at her request in order to maintain her reproductive function. The twenty-three patients whose only treatment thus far has been cauterization have been followed most carefully, and we are certain that they are free of their disease at the present time. These cases unintentionally treated by cauterization and cured merely demonstrate that it can be done.

I somewhat disagree with Dr. Schwarz about biopsy versus conization. In our hands biopsy is accurate. We include a cervical curettage saving for the pathologist the blood clot as well as the tissue. No one at our hospital can conize a cervix and not get a high incidence of postoperative stenosis except Dr. Rock.

So far as breaking the news to the patient, it has been my responsibility to follow these patients. We insist that they have two or three positive biopsies at one- to two-month intervals before any treatment is done because in some of them the diseased is appears. It is explained to them that they have a condition about which pathologists disagree, but we personally feel that it may develop into cancer in the course of one to five years. It is explained to them that there is a long period of safety and that study is necessary in order to avoid an unnecessary hysterectomy. Our patients have been very cooperative and only a few have demanded treatment immediately. We are now following over thirty patients with anaplasia or questionable carcinoma in situ of the cervix. We do not want to do a hysterectomy on them at the present time because they are all young.

From our experience with carcinoma in situ of the cervix a radical hysterectomy is not necessary if the disease is evaluated carefully before operation.

RESULTS OF AN EXPERIMENTAL THERAPY OF CARCINOMA OF THE CERVIX*

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IT IS generally agreed that irradiation therapy of cervical carcinoma offers the most effective therapeutic approach presently available. That it is not an ideal solution to therapy is obvious. But until a better approach becomes available, the therapeutic tools which are at hand must be used with a maximum efficiency. A great variety of techniques is being used. These show variations in time factors, in dosage and the accuracy with which this is determined and reported, in the relative stress given to x-ray and to radium and in the technical details of controls and patient care. It has been publicly stated that all of these are producing similar results but a careful examination and biometric testing of reported results show that this is not so. Since statistically significant differences can be demonstrated, it would seem essential that the details which led to such differences be carefully examined with the object of establishing wherever possible at least general principles which can be accepted. There are many difficulties which lie in the path which leads to such a goal; but one has only to look at the older figures from the League of Nations reporting clinics and to compare them with what is being achieved today to realize that enormous improvement has been made. The door is not closed to still further progress.

The present report deals with part of a larger study which has been going on since 1939. This report deals only with the results of therapy. The techniques and dosages which were chosen for the study are admittedly arbitrary and were applied after some preliminary exploration. There is no adequately based theory on which to determine the finer details although much interesting work has been done in this field. This is not the place to argue the theoretical advantages or disadvantages concerned. It was decided to apply deep x-ray daily except Sunday over as close to twenty-eight days as possible and to follow this immediately by the application of radium. Clinical experiments were run to determine the dosages of each which under these circumstances would be tolerated by the average patient. With minor variations, as individual study programs arose, this has been carried out on the whole group.

It was decided to deliver 3,000 tissue roentgens by x-ray diffusely to the whole pelvis including the tumor over as close to twenty-eight days as possible. Each patient is measured and, by the application of standard charts,

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the number and size of fields and the amount of irradiation given per treatment are determined. In preliminary studies, ionization chambers were placed in the craters of suitable tumors and the reality of the dosage determined. There is a very considerable variation between the calculated and the actual dose to the tumor area even under circumstances where accurate calculations are made. To guess what the tumor area gets from some arbitrary decision as to the dosage which is given to arbitrarily determined sizes of skin fields is a method so grossly inaccurate that it should not be used. It usually results in gross underdosage for purposes of medicolegal safety which is a poor basis for determination of dosage. In the earliest part of the study the tumor dosage often fell between 2,600 and 3,000 tissue roentgens because of fear of the larger dosage. Recently, as a separate study, the League of Nations Stage III tumors have been treated with a total of 3,500 tissue roentgens. There are not enough of either of these to influence significantly the end results.

During the time under consideration, relatively small changes in the roentgen therapy technique have been made. Between January, 1939, and June, 1942, the factors were: 220 kv., 1 mm. copper + 1 mm. aluminum filter, half value layer 1.7 mm. Copper; 60 and 70 cm. target-skin distance. Since June, 1942, the factors have been: 400 kv., .44 mm. tin + .25 mm. copper + 1 mm. aluminum filter, half value layer 3.9 mm. copper; 70 and 80 cm. target-skin distance.

As a rule, five fields were used: one anterior 18 by 20 cm., one posterior right oblique 14 by 18 cm., one posterior left oblique 14 by 18 cm., one right lateral 12 by 18 cm., and one left lateral 12 by 18 cm. One field was treated each day, 300 to 350 r./air. A total dose of 3,000 tissue roentgens was given to the center of pelvis in a period of 28 days. All these factors were, of course, varied somewhat to suit the individual. The only thing that was supposed to remain constant was the calculated dose of 3,000 tissue roentgens to the center. At first the dose was, however, somewhat lower and was gradually raised from a minimum of 2,500 to a routine of 3,000 tissue roentgens. An effort was made to limit the time to 28 days but a variation became necessary from about 25 to 35 days. Patients with large anterior-posterior and lateral diameters were given additional fields (perineal, anterior oblique fields). Two fields were sometimes treated the same day. Complications such as a drop in the patient's white blood count below 2,000, fever, or symptoms of uremia made it occasionally necessary to interrupt the treatments for a few days.

With 3,000 tissue roentgens to the center, a higher dose was obtained in certain portions of the pelvis and the maximum reached about 3,600 tissue roentgens.

The radium dosage, as in all other surface radium irradiation in the Department of Obstetrics and Gynecology, has been given over 100 hours. This is an arbitrarily chosen time with some vague theoretical advantages. But the standardization allows avoidance of one variable in the relationship between physical and biological dosage and so aids in accuracy. Multiple radium portals are used in order to get a maximum dose at as great a distance in the lymphatic drainage system as possible while still remaining within the tolerance of the local tissue which must be left so that it will heal. Compound isodose curves for an ideal setup show the cervical tumor itself to receive 15,000 to 25,000 gamma roentgens. This is more than is required and is not the determining factor in dosage. The cervix and vagina in the well-nourished

patient will tolerate this and heal. A Kaplan colpostat is used in the vagina with as many portals to a maximum of three as the individual vagina will take. Radium in tandem is placed in the uterine cavity in an uncovered platinum container 5 to 6 cm. in length. One millimeter of platinum or its equivalent filtration is used. The vaginal colpostat has approximately 0.75 cm. of focal distance. When anatomically possible, two portals in tandem of 10 mg. of radium each are used in the uterus and three similar portals in the two arms and the central cork of the Kaplan colpostat in the vagina. Thus 50 mg. are applied for 100 hours. This dosage will vary somewhat with individual circumstances of the tumor and the patient. The dosage is of necessity decreased as the number of portals has to be decreased in the presence of vaginal shrinkage or absent uterus. The radium is applied on the day of the last x-ray treatment and is held in position by gauze moistened by an emulsion of 1 per cent neutral acriflavine to decrease bacterial growth.

The patients are hospitalized throughout the whole course of therapy. They are fed a high-protein, antianemic, low-residue, high-caloric diet. The usual studies are carried out to recognize abnormalities and usual treatment carried out for these when they occur.

The material consists of all patients who have come under control of the department from January, 1939, to the end of 1947. The League of Nations Cancer Committee rules have been applied and their staging used. Thus all patients with carcinoma of the cervix who have come to the gynecological department have been considered but those who had been treated previously for this condition are placed in a separate group referred to as nonreportable cases. A few patients have been excluded. Those who have been treated elsewhere and have come for follow-up are not included if they showed no tumor and so were not treated by this department. Almost all of the reportable cases had had no previous treatment. Two patients are included as reportable though a biopsy was taken elsewhere, a negligible quantity of radium applied, and the patients immediately referred. This was not considered as treatment elsewhere since it was not such as to be taken into any consideration in our own therapy and did not interfere for more than a few days with referral.

The patients with adenocarcinomas of the cervix are included since, surprisingly enough, they showed similar results to those with the squamous-cell tumors and so do not influence the conclusions. The three adenoma malignum cases all fall into the nonreportable group.

Every patient has been followed to death or to January, 1949. The department has been fortunate in the availability of funds to support a full-time trained secretary whose only duty is the organization of the follow-up of the gynecologic malignant disease patients. Multiple addresses of relatives and friends, preferably those who own property or are otherwise relatively geographically fixed, are taken on recognition of the tumor and this list is kept up to date. It is a simple procedure which has been of significant aid in an otherwise difficult and uncertain task.

The diagnosis has been made or confirmed by biopsy in every case. For all of those who have passed five years since treatment, the histologic material has been passed upon by the late Dr. Robert Meyer. There is no questionable carcinoma in the series.

A few patients have been treated by primary surgery for a variety of reasons. There were but seven of these and only two of them were treated more than five years ago. The results in these do not vary from the results in the general group sufficiently to change the rates. They are left in with the irradiation group for completeness.

In addition, there were eight patients who were treated more than five years ago by irradiation followed by surgery and two in whom the tumor was microscopic and found in the surgical specimens. These latter were irradiated after surgery. Five of these ten were alive and free of tumor at the end of five years. Since they, again, do not change the figure for the general material, they are included.

Results

The results are shown in Tables I to V. The absolute five-year cure rate is 53.6 per cent (S.D. ± 2.8 per cent). For Stage I, this was 80.2 per cent (S.D. ± 4.0 per cent); for Stage II, 54.1 per cent (S.D. ± 4.8 per cent); for Stage III, 29.5 per cent (S.D. ± 5.2 per cent); and in Stage IV, a single patient of 16 survived. The standard deviations were determined on each year's survival figures. The proportions of the total material in each of these stages is shown at the bottom of the tables.

Two patients with Stage III tumors were not treated. One refused and one died with uremia and septicemia before treatment could be begun. Six patients with Stage IV tumors were not treated. Four of these had hopeless distant metastases and two died of intercurrent disease before treatment. All of these are included in the calculation of the absolute survival rate. All are dead. An attempt was made to treat all others but, for various reasons, a further 15 patients had therapy which was stopped before what could be considered adequate therapy had been delivered.

TABLE I. REPORTABLE CARCINOMA OF CERVIX UTERI, STAGES I-IV. ABSOLUTE RESULTS

	PATIENTS		SURVIVAL IN YEARS 1	2	3	4	5	6	7	8	9
1939	52	No.	48	42	38	36	35	34	33	32	31
		%	92	81	73	69	67	65	63	61	60
1940	68	No.	47	40	36	36	34	34	32	32	
		%	69	59	53	53	50	50	47	47	
1941	72	No.	55	43	36	34	34	31	31		
		%	76	60	50	47	47	43	43		
1942	61	No.	49	42	39	37	35	33			
		%	80	69	64	60	57	54			
1943	44	No.	33	26	21	21	21				
		%	75	59	48	48	48				
1944	70	No.	53	43	37	35					
		%	76	61	53	50					
1945	71	No.	48	44	36			Irradiation alone, 287			
		%	68	62	51						
1946	58	No.	42	34				Irradiation plus surgery, 10			
		%	72	59							
1947	81	No.	60								
		%	74								
Irradiation total			577	496	438	367	297	253	192	120	52
Survival			435	314	243	199	159	132	96	64	31
Absolute percentage			75	63	55	54	53.6	54	50	53	60
Surgery only			7	6	5	3	2	2	2	2	2
Survival			5	5	4	2	1	1	1	1	1
Total absolute			584	502	446	373	299	251	194	122	54
Survivals			440	319	247	201	160	133	97	65	32
Absolute cure rate			77	64	55	55	53.6	53	50	53	59
Patients seen 1939-1943							299				
Patients treated 1939-1943							291				
Relative cure rate							55%				

TABLE II. REPORTABLE CARCINOMA OF CERVIX UTERI, STAGE I. ABSOLUTE RESULTS

PATIENTS			SURVIVAL IN YEARS 1	2	3	4	5	6	7	8	9
1939	15	No.	15	15	15	15	15	14	13	12	12
		%	100	100	100	100	100	94	87	80	80
1940	16	No.	14	14	14	14	14	14	13	13	
		%	87	87	87	87	87	87	81	81	
1941	22	No.	21	18	15	15	15	14	14		
		%	95	82	68	68	68	64	64		
1942	28	No.	27	25	23	22	22	21			
		%	96	89	82	78	78	75			
1943	13	No.	12	11	10	10	10				
		%	92	85	77	77	77				
1944	12	No.	11	11	10	9					
		%	92	92	83	75					
1945	15	No.	15	13	13			Irradiation alone, 86			
		%	100	87	87						
1946	23	No.	18	16				Irradiation plus surgery, 8			
		%	78	70							
1947	36	No.	31								
		%	86								
Irradiation total			180	144	121	106	94	81	53	31	15
Survival			164	123	100	85	76	63	40	25	12
Absolute percentage			91	85	83	80	81.1	78	76	81	80
Surgery only			5	5	5	3	2	2	2	2	2
Survival			4	4	4	2	1	1	1	1	1
Total absolute			185	149	126	109	96	83	55	33	17
Survivals			168	127	104	87	77	64	41	26	13
Absolute cure rate			91	85	83	80	80.2	77	75	79	76

TABLE III. REPORTABLE CARCINOMA OF CERVIX UTERI, STAGE II. ABSOLUTE RESULTS

PATIENTS			SURVIVAL IN YEARS 1	2	3	4	5	6	7	8	9
1939	19	No.	18	14	11	10	10	10	10	10	10
		%	95	74	58	53	53	53	53	53	53
1940	31	No.	25	21	17	17	17	17	16	16	
		%	81	68	55	55	55	55	52	52	
1941	26	No.	23	18	15	14	14	12	12		
		%	88	69	58	54	54	46	46		
1942	15	No.	13	10	10	10	9	8			
		%	87	67	67	67	60	53			
1943	18	No.	14	12	9	9	9				
		%	78	67	50	50	50				
1944	31	No.	25	21	18	17					
		%	81	68	58	55					
1945	29	No.	27	21	16			Irradiation only, 107			
		%	93	72	55						
1946	18	No.	14	12				Irradiation plus surgery, 2			
		%	77	67							
1947	27	No.	20								
		%	73								
Irradiation total			214	187	169	140	109	91	76	50	19
Survival			179	131	96	77	59	47	38	26	10
Absolute percentage			84	70	57	55	54.1	52	50	52	53
Surgery only			2	1	0						
Survival			2	1	0						
Total absolute			216	188							
Survivals			181	132							
Absolute cure rate			84	70							

TABLE IV. REPORTABLE CARCINOMA OF CERVIX UTERI, STAGE III. ABSOLUTE RESULTS

IRRADIATION ONLY PATIENTS			SURVIVAL IN YEARS								
			1	2	3	4	5	6	7	8	9
1939	17	No.	14	12	11	11	10	10	10	10	9
		%	82	71	65	65	59	59	59	59	53
1940	15	No.	7	4	4	4	2	2	2	2	
		%	47	27	27	27	13	13	13	13	
1941	23	No.	11	7	6	5	5	5	5		
		%	48	30	26	22	22	22	22		
1942	12	No.	7	6	6	5	4	4			
		%	58	50	50	42	33	33			
1943	11	No.	7	3	2	2	2				
		%	64	27	18	18	18				
1944	24	No.	16	11	8	8					
		%	67	46	33	33					
1945	21	No.	16	10	7						
		%	76	47	33						
1946	13	No.	9	5							
		%	69	38							
1947	13	No.	6								
		%	50								
Irradiation			149	136	123	102	78	67	55	32	17
Survival			93	58	46	35	23	21	17	12	9
Absolute percentage			62	43	38	34	29.5	31	31	38	53

TABLE V. REPORTABLE CARCINOMA OF CERVIX UTERI, STAGE IV. ABSOLUTE RESULTS

IRRADIATION ONLY PATIENTS			SURVIVAL IN YEARS								
			1	2	3	4	5	6	7	8	9
1939	1	No.	0	0	0	0	0	0	0	0	0
		%	0	0	0	0	0	0	0	0	0
1940	6	No.	1	1	1	1	1	1	1	1	
		%	16	16	16	16	16	16	16	16	
1941	1	No.	0	0	0	0	0	0	0		
		%	0	0	0	0	0	0	0		
1942	6	No.	2	1	0	0	0	0			
		%	33	16	0	0	0	0			
1943	2	No.	0	0	0	0	0				
		%	0	0	0	0	0				
1944	3	No.	1	0	0	0					
		%	33	0	0	0					
1945	6	No.	0	0	0						
		%	0	0	0						
1946	4	No.	1	1							
		%	25	25							
1947	5	No.	2								
		%	40								
Irradiation total			34	29	25	19	16	14	8	7	1
Survival			7	3	1	1	1	1	1	1	0
Absolute percentage			21	11	4	5	6	7	12	14	0

The individual types of tumor will be the subject of separate study but it might be worth noting here that considering only those who have passed the five-year interval since treatment, 52 per cent of 274 patients with squamous-cell tumors, 50 per cent of 10 with adenocarcinomas of the cervix, and 69 per cent of 13 with squamous-cell carcinomas of the cervical stump were alive and clinically free of tumor after this interval.

The patients with nonreportable tumors, or those who had been treated elsewhere prior to observation in the Department of Obstetrics and Gynecology of the University of Minnesota show little of interest. They are not grouped under the League of Nations four stages but those described as local tumors

are roughly comparable to Stages I and II while the extensive tumors correspond to Stages III and IV.

NONREPORTABLE CARCINOMA OF THE CERVIX

		5 YEAR SURVIVAL, FREE OF TUMOR
"Local"	14 patients	8 or 57 per cent
"Extensive"	31 patients	3 or 9.7 per cent
Total	45 patients	11 or 24 per cent

Comment

The results of treatment of cervical carcinoma prior to 1939 have not been listed. As in other clinics, these show a steady improvement with no significant change in degree of clinical extension of the tumors over the years. Toward the end of this period about half the x-ray dosage and two-thirds of the radium dosage which has been given in the present study series were exhibited. The present study series shows a significantly greater cure rate. The cure rate reported here is significantly greater than that reported by a number of other investigators using different techniques but has been equaled by still others.

One would like answers to two questions. What are the significant features of the present techniques which have improved the results in our own material? What are the circumstances under which failure occurs and what next move might be made to recognize and attack these?

There is at present no simple answer to these questions. On the other hand, there can be no doubt but that gradual and steady improvement in end results is being made. The actual problem lies in what could be called the critical group of tumors or those which can be almost cured by a given technique. This involves a very few Stage I tumors but considerable numbers of Stages II and III. It is here that attention to detail and accuracy will yield a reward in producing the difference between ordinary and good results.

In this critical or borderline group, there can be little question but that accuracy of x-ray dosage to the tumor plays a significant role. The dosage which can be delivered to the tumor is limited by the tolerance of the intervening normal structures. It is only a fraction of that which has been experimentally determined as a so-called "tumor destructive dose." Because of the inevitable short focal distance of the vaginal and uterine radium application, and the inverse square of the distance law which limits the amount of irradiation energy delivered to depth, one is largely dependent on the x-ray with only a small contribution from the radium for the destruction of tumor at distance in the pelvic lymphatic system. Overdosage may destroy the patient directly, or, what amounts to the same thing, so interfere with normal tissue healing that its contribution in the final choking off of partially damaged tumor cells is interfered with and tumor recurrence results. Underdosage can lead to an occasional cure but the possibilities, particularly in this critical group, are not exhausted. Calculation of dosage, then, should start with the area at depth to be treated. Our studies have shown that a diffuse dose to the pelvis of 3,000 to 3,500 tissue roentgens over about 28 days represents the maximum reasonably safe dose. The dosage to skin, the sizes and numbers of fields, are calculated for each patient to supply this. This should also be the basis for reporting. The total amount of irradiation energy supplied to the skin is not a useful expression of the tumor dose. An accurate expression of depth dose is essential. If there be any doubt about the inaccuracy of the tumor dose which is based on a guess as to how many units should be given to the skin, the actual measurement of the dose which arrives at the cervical tumor is a simple undertaking and may prove surprising. It is true

that what is finally required is an expression of effect on the tumor or of biological dosage and that this is varied by many other considerations than dosage expressed in physical units alone. But unless this latter is as accurate as possible for the tumor-bearing area at depth under consideration, then all subsequent controls of accuracy fail. To interpret into a tumor dose the statement that 10,000 roentgens in air have been given to the skin produces a sense of frustration not unlike reaching out the window for the moon.

A similar word of warning should be said in regard to radium dosage. Again, the biological effect and not the physical dosage must be considered. Both normal tissue and tumor recover from the effects of appropriate amounts of irradiation energy. Unfortunately, there is reason to believe that the recovery of tumor from sublethal doses is more rapid than that of normal tissue. If this were the only factor concerned, the more rapid the delivery of a tolerated dose, the greater the advantageous differential of sensitivity might be expected to be. Clinical testing of this has led to the conclusion that there are other factors concerned and that something between single dose and infinitely prolonged therapy is desirable. It was somewhat arbitrarily decided to use for this study continuous therapy with about 28 days of x-ray followed immediately by 100 hours of radium application. The time factor is excluded as a variable from one patient to another. The results which it has produced are presented. They seem to have been significantly better than the reported results of some other types of time distribution and consequently are recommended. To prove that this is the most important feature of the results obtained is of course impossible.

The value of hospitalization throughout treatment is difficult to assess. It is expensive. But it allows the early recognition of sometimes dangerous disturbances. It has allowed treatment of the tumor to be driven through where considerations of safety would have demanded interruption in the outpatient. It has allowed dietary control, particularly of the protein intake, which may well be important, and which is now being studied. In general, it contributes to the accuracy of the handling.

In what direction should one turn for further improvement? It is obvious that surgery and irradiation must both eventually be supplanted by a more effective attack. In the meantime, the search must go on for methods of improving the effectiveness of the tools which are presently available. There can be no doubt but that accurately applied irradiation offers the most effective of such tools and that the surgical approach should be restricted to special circumstances. The problem now is to define objectively these special circumstances and some progress is being made here. It is hard to become concerned about the very early tumors since they can be effectively treated by either surgery or irradiation. Irradiation has consistently failed with the Stage IV tumors in spite of the fact that in a significant proportion of them, the host may be destroyed while the tumor is still apparently localized to nonvital though useful pelvic structures. Information as to the effectiveness of very radical surgery for these tumors must be obtained as soon as possible. Most gynecologists have satisfied themselves that this sort of procedure can be done with reasonable safety and not too much in the way of undesirable aftereffects.

The study of the material here reported makes it perfectly clear that the greatest single improvement may be expected to come from the solution to two problems. Some method must be found which will allow recognition at least by the time therapy is complete of those tumors which will fail to respond to irradiation. Histological studies on material taken on the day x-ray is completed and radium applied have been of questionable value in our hands. And, second, one cannot study such material as is presented here without being

impressed by the relationship between the size of the tumor and its local persistence after irradiation. The large extensive tumor may, on microscopic study, look the same as others before treatment and apparently respond similarly to the same dose of irradiation only to persist locally with an exasperating frequency. There is too much detail for presentation here but it might be pointed out that of the fifty patients with Stage III carcinomas of the cervix in this series who died as a result of the tumor, only five were known to have died with the pelvis free of tumor. There is a strong suggestion of some interference by the massive tumor with normal tissue healing ability. Control of this difficulty would be extremely valuable.

Summary

1. Carcinoma of the cervix has been treated at the University of Minnesota Hospitals since the beginning of 1939 by means of daily x-ray therapy followed immediately by intravaginal and intrauterine radium. X-ray is given over as close to 28 days as possible and the details of this therapy are arranged so as to supply 3,000 tissue roentgens diffusely to the pelvis in this time. This is followed on the day of the last x-ray treatment by the insertion of radium which is left in place for 100 hours. Under ideal anatomical circumstances, two intrauterine portals in tandem and three vaginal portals in the Kaplan colpostat are used. Each contains 10 milligrams of raduim for a total dosage of 5,000 milligram hours. This is decreased as the availability of space for these portals is decreased.

2. Every single patient has been followed to death or to Jan. 1, 1949. Every single patient has satisfactory biopsy control. There is no questionable carcinoma in the material.

3. The following results have been obtained on reportable material. The League of Nations classification is used.

Absolute five-year cure rate, 53.6 per cent (S.D. ± 2.8 per cent)
Stage I, five-year cure rate, 80.2 per cent (S.D. ± 4.0 per cent)
Stage II, five-year cure rate, 54.1 per cent (S.D. ± 4.8 per cent)
Stage III, five-year cure rate, 29.5 per cent (S.D. ± 5.2 per cent)
Stage IV, only 1 patient of 16 cured.

4. Adenocarcinomas, carcinomas of the cervical stump, and a few cases which were treated with surgery as well as x-ray are included. Because of their small number and the surprising similarity of the results with them to those of the general group of squamous-cell carcinomas, they do not influence the expression of results.

5. The techniques described have significantly improved the results previously obtained and are recommended.

The essential follow-up studies on which this report is based were only possible because of financial support generously made available by the Minnesota Division of the American Cancer Society, Inc.

Discussion

DR. DANIEL MORTON, San Francisco, Calif.—The results which Dr. McKelvey has reported are excellent. Indeed, they are better than any that I know of. In attempting to account for the superiority of his figures one will naturally ask oneself certain questions.

First, are there features of the treatment technique itself which set it apart from others and to which one may attribute an improved response? Second, are there other factors inherent in the material which might be responsible? In answer to the first question, Dr. McKelvey has pointed out that certain features of the treatment and general management of the patients have been fairly constant, and therefore deserve attention as possible contributors to the excellence of the results. I refer to (1) the fixed plan of irradiation, involving as it did a set dose of both x-ray and radium given over exactly the same length of time in each individual case, and (2) hospitalization during the entire treatment, allowing for careful observation, prompt treatment of anemia, infection, etc., and proper nutrition. I am not certain that a fixed plan of irradiation is actually superior to one involving some individualization, provided that the individualization is adminstered by one who thoroughly understands the problem. However, the fixed plan which was followed seems to have been a happy one, involving reasonably adequate doses of both x-ray and radium, in favorable proportions. Since the fixity in the time element was the most constant and outstanding feature of the irradiation we cannot fail to recognize its possible importance. Hospitalization during treatment is of definite value, I am sure. The biggest drawback to such a plan in most institutions and for most individuals is the expense, not only in money, but in bed space. Nevertheless, I believe that the results at Minnesota are sufficiently outstanding to stimulate more adherence to such a plan.

With regard to the second question, I should like to exhibit the following table which compares material and results from the Minnesota Clinic with those from the University of California Clinic, and the composite figures in the last (collated in 1939) Annual Report of the League of Nations Health Organization.

	CASES INCIDENCE OF THE VARIOUS STAGES						FIVE-YEAR SURVIVALS IN PER CENT		
	MINN.		CALIF.		L. OF N.				
STAGE	NO.	%	NO.	%	NO.	%	MINN.	CALIF.	L. OF N.
I	94	(31.6)	114	(20.5)	1,280	(11.6)	81.1	65	56.1
II	109	(36.6)	197	(35.8)	3,054	(27.8)	54.1	48	37.3
III	78	(26.3)	177	(31.9)	4,414	(40.2)	29.5	24	22
IV	16	(5.4)	67	(11.8)	2,220	(20.2)	6	4.4	4.4
	297		555		10,970		53.6	39.9	26.7

It is obvious that the group of cases reported by Dr. McKelvey contains a much lower proportion of advanced cases (Stages III and IV) than do either of the other two series. This in itself will inevitably make a considerable difference in the final salvage in favor of the Minnesota series. In turn, the University of California material is better than that represented by the composite figures, and in turn the five-year salvage is considerably better. Perhaps there have been differences in interpretation of what constitutes the various stages of advancement; however, such differences could hardly account for the vast differences in the figures. I would like to believe that education is responsible for more and more earlier diagnoses. If this is true then we must compliment Minnesota for being so outstanding in this respect.

Another point of interest in the comparison is that Dr. McKelvey's results are also superior in the individual stages. This may be due to actual superiority in the technique of treatment, as discussed previously. It is not entirely understandable, however, since the greatest superiority is noted in the early stages, especially Stage I, in which differences in technique should have the least effect. I would like to suggest that Minnesota women may be more responsive to irradiation than some others. This is not meant to be facetious since vast differences in tissue and tumor susceptibilities to irradiation, due to unknown factors, have long been recognized.

It is my belief, then, that the superiority of the results reported should be attributed not only to the technique and management employed, but also to other factors which relate specifically to the type of material involved, and possibly to other unknown factors.

DR. CHARLES A. BEHNEY, Philadelphia, Pa.—Dr. McKelvey's paper gave me the impression that perhaps his better results may have, at least in part, been due to his extreme

care in securing adequate irradiation and in supervising the general health of his patients. All too often we are inclined to regard a patient who has carcinoma as "another case of cancer" and to neglect diet, the condition of the blood, etc. It is well known that anemic patients tolerate irradiation badly. Fat women with thick abdominal walls require more irradiation to the skin, to treat the cervix adequately, than do thin women. X-ray equipment must be standardized at regular intervals of at least every six months. These machines get out of order and deteriorate. As connections become less efficient and the tubes get older, the exposure time must be increased in order to deliver the same dosage as when the equipment was new. In the case of radium filtration, the distance between the radium tube and the lesion being treated must be taken into consideration as well as the time during which the radium is applied.

DR. KARL WILSON, Rochester, N. Y.—I would like to see a little more attention paid to the selection of radioresistant tumors, and that is a difficult thing to do. The histology is not the entire picture. You take a biopsy and you think the tumor is radiosensitive. You treat that patient by irradiation therapy and the result is not what you want so you say it was radioresistant.

It has been our custom for the last year in the follow-up of treated patients to take repeated vaginal smears again and in general we find that when a patient has been successfully treated, the smear quickly becomes negative. On this basis I am not prepared to make a positive statement but I suspect that if, eight weeks afer irradiation therapy has been completed, we can still demonstrate cancer cells, we regard it as radioresistant, and that may be the group of patients who may be suitable for surgical treatment of their carcinoma in Stage I or II cases.

DR. WILLIAM P. HEALY, New York, N. Y.—This report is most stimulating, at least to us who carry out irradiation therapy in the treatment of carcinoma of the cervix. Dr. McKelvey has presented the best end results we have heard of. I was very much interested and pleased with the point he makes of preliminary roentgen irradiation. This is carried out in his cases first and is finished before radium is applied. At the Memorial Hospital we brought that out many years ago. We emphasized also the importance and value of biopsies taken at intervals during the course of roentgen therapy to show the regressive effect of such treatment on the tumor. I was interested in the fact that on the last day of roentgen therapy they start radium therapy. We have found it desirable with a similar amount of roentgen therapy to delay the radium application about ten days.

Dr. McKelvey emphasized that adenocarcinoma and squamous carcinoma of the cervix respond in a similar way to irradiation therapy. We have found that this is true: that there is no difference whatsoever in response of adenocarcinoma or squamous carcinoma; that the response depended entirely upon the clinical classification of the case and not on the histologic structure of the tumor.

I think that possibly one of the most important factors in his excellent end results is the fact that his patients are hospitalized throughout their term of therapy. That must be a very important item in leading to better end results. We could not do that for the same reasons stated by Dr. Morton, but I do think that having the patient under the observation of one competent person or a team of two or three competent men throughout the course of therapy and under close observation after hospitalization will increase the percentage of favorable results.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—I shall only emphasize one phase and that is the use of preliminary x-ray irradiation. At the Jefferson Clinic we have found, after we had gotten away from the hit-or-miss use of radium and x-ray interchangeably, in the series which we could evaluate most recently on the basis of adequate x-ray irradiation, that our over-all results had increased from 25 to 38 per cent, in spite of the fact that our Stage I and II cases together are in the neighborhood of only 12 per cent. We also can evaluate on a five-year basis a series of cases in which both external and transvaginal irradiation was used as a peliminary to radium and this group has shown no increase in salvage results with respect to the addition of the transvaginal route.

DR. JOSEPH BAER, Chicago, Ill.—Will the speaker evaluate what continuous hospitalization does which cannot be done on an ambulatory basis with a carefully observed record?

DR. McKELVEY (Closing).—It is impossible to be certain of the significance of any one specific factor. This study was designed to test a given set of circumstances. I do not know why there are so many early cases in this material but I think I know one reason. I am satisfied that in those Departments of Gynecology where the histology on material obtained from the clinic is checked by a gynecologist there is an increase in the number of early cases found. More of the tissue is likely to be examined. The material presented today passed through both the Departments of Gynecology and Pathology and separate reports were placed on the record. There are some tumors which have been found by smear but none of this material appears in this five-year cure group.

There is no question but that meticulous care of the patient and of the irradiation details pays off. It appears that the amount and time distribution of dosage play a part but it is impossible to prove it.

Dr. Wilson put his finger on one important problem. How can we recognize those tumors that will be radioresistant? The histologic study of the tumor immediately after x-ray therapy is completed has not proved accurate in our hands. It would be of enormous value to be able to recognize early those tumors which will recur locally. No accurate method is presently available. A study on the effect of protein feeding is now under way. We know what part protein plays in major surgery and perhaps it does the same here too. Local recurrence of tumor may well be due to a deficiency of normal tissue response rather than tumor resistance to irradiation energy. The adequacy of normal tissue nourishment could be very important itself.

Follow-up smear study has been useful. It will recommend itself to all who have attempted to deal with biopsy material from patients who have been irradiated. The difficulty of obtaining adequate biopsy material and often of interpreting it is common knowledge.

Dr. Baer has asked for an evaluation of continuous hospitalization for these patients. In answering this, it should be pointed out that the dosage which was used was clinically determined. There is considerable experience with lower dosages and the older material at the University of Minnesota Hospitals was used for this control. Larger dosages than those here reported have been used by the author experimentally. These produced too frequent damage. The conclusion was that even the massive dosage used on the patients reported here produced on occasion sufficiently serious disturbances to require hospitalization for early recognition and treatment. It was twice the dosage previously used and, frankly, we are afraid to give it without detailed observation. There are many patients in whom, because of their specific circumstances, one would not dare to continue massive therapy without close observation. It appears to be very important to avoid interruption of the course of therapy, and hospitalization has helped in accomplishing this. Agranulocytic leucopenia is of sufficiently frequent occurrence to justify hospitalization. Those who have seen these patients die of leucopenia will agree that daily determination of white blood cell counts under exactly similar circumstances is necessary. It is difficult to interpret white counts taken at any time of the day.

It is hard to avoid being convinced that diet plays a part, probably in maintenance of normal tissue response to the tumor area. All have seen the cachectic patient with a great tumor that can be blown out with irradiation therapy but which simply continues to grow from the margin. Local tissue reaction is important and the dosage given must be kept under the amount which results in destruction of normal tissue. But local tissue nourishment is probably equally important. Have you tried to force food into these patients? It cannot be done adequately at home but can be accomplished by trained hospital staffs. It is astonishing to realize how much can be done by explaining these things to the patient.

It is admitted that this has been an expensive form of therapy but in our experience it has paid off by comparison with other techniques used. There are better bases than cost on which to determine the details of malignant disease therapy.

FURTHER STUDIES ON THE EFFECT OF IRRADIATION THERAPY FOR CARCINOMA OF THE CERVIX UPON THE URINARY TRACT*

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IN 1939 we reported our observations upon the effects of carcinoma of the cervix and its treatment upon the urinary tract. In that study we had attempted to examine urologically patients subjected to irradiation therapy for carcinoma of the cervix before the institution of treatment and at various intervals ofter completion of therapy. Forty-six patients were so studied before treatment, and the conclusion drawn from that study was that evidence of ureteral obstruction before the institution of treatment constituted an extremely grave prognostic sign.

Since some of the patients studied before treatment died before sufficient time had elapsed to make posttreatment studies worth while, and as others failed to cooperate, only 33 patients were studied urologically subsequent to completion of irradiation therapy. Of these, 16, or 48.4 per cent, showed some evidence of ureteral obstruction and 18, or 54.5 per cent, some type of bladder lesion. In only about 15 per cent, however, were the ureteral obstructions sufficiently severe to be of clinical importance, and in only 20 per cent were the bladder lesions of serious clinical significance.

At the time of this report less than five years had elapsed in most of the patients since the irradiation therapy had been administered, but as they appeared to be clinically well of carcinoma it was assumed that the effects observed upon the urinary tracts were the result of irradiation damage rather than of persistent or advancing carcinoma. We have felt that it is now worth while to restudy and re-evaluate this group of cases to determine to what extent we were right in assuming freedom from carcinoma and therefore assigning the urological lesions to irradiation damage. In the course of this restudy we have found that one patient originally designated as exhibiting only a mild bladder reaction has subsequently developed very dense ureteral strictures, and another patient, who at the time of the original report showed no urological lesions, as late as 1946 developed vesicovaginal and rectovaginal fistulas and complete occlusion of one ureter with large hydroureteronephrosis on the opposite side (Fig. 1).

*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

For this study we have divided the patients into three groups according to the location and nature of the original lesions (Table I). From this table it will be seen that there were 13 patients in whom the evidence is practically incontestable that the carcinoma was cured.

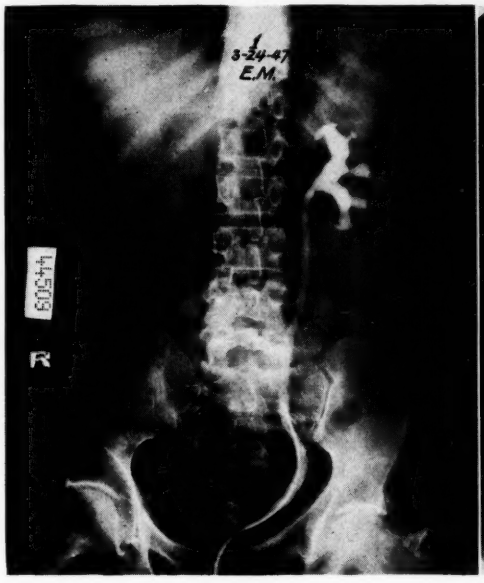

Fig. 1.

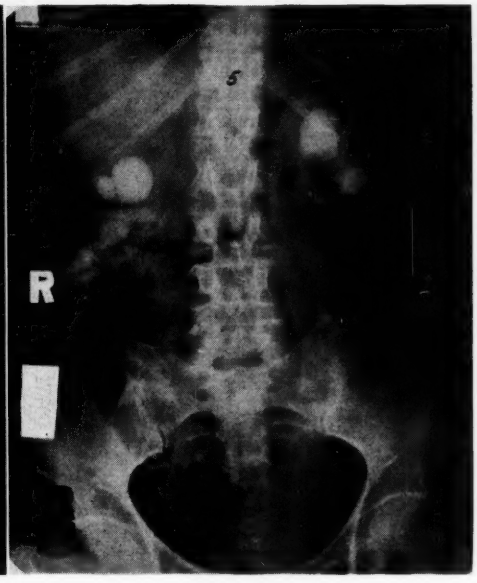

Fig. 2.

Fig. 1.—E. M. (Case 118897), treated for Stage II carcinoma of cervical stump in July and August, 1937. In 1939 the patient was apparently well and showed no evidence of urological complications. In 1946 she developed a large vesicovaginal fistula with complete occlusion of the right ureter. The pyelogram made March 24, 1947, shows evidence of stenosis of the left ureter in the intravesical portion. The patient has been treated by repeated dilatations of this stenosis.

Fig. 2.—C. Z. (Case 127093). Thirty-three minute intravenous pyelogram made three years after treatment with 2,600 mc. hr. of radium emanations for supposed Stage III carcinoma. At the time of this examination the patient had been suffering for more than a year from an intense ulcerative cystitis with encrustations. The films taken earlier than thirty-three minutes showed little visualization. (From Everett, H. S.: Am. J. Obst. & Gynec. 38: 889, 1939.) Subsequent to this report this patient developed vesicovaginal and rectovaginal fistulas. She died of uremia fifty-seven months after treatment and autopsy revealed no remaining carcinoma.

The present or ultimate status of the urinary tracts in these 13 patients is shown in Table II.

Shortly after the completion of the study reported in 1939, the technique of irradiation therapy, especially that of radium administration in our clinic, underwent a radical change. The patients included in the 1939 report had been treated as ambulatory patients with the rapid administration of irradiation using large quantities of radon. The total dosage administered to each patient varied considerably, but in nearly all cases was considerably less than that which we are giving now. An average dose was 3,000 mc. hr. administered by the use of 3 gm. equivalents of radon for a period of one hour. Many of the patients with early lesions received no x-ray therapy. The exact dosages received by all patients ultimately showing evidence of urinary tract damage are contained in the tables in the 1939 report.

TABLE I. PRESENT STATUS OF CASES SHOWING UROLOGICAL LESIONS FOLLOWING IRRADIATION FOR CARCINOMA OF THE CERVIX, REPORTED IN 1939

LOCATION OF LESIONS	TOTAL PATIENTS	BLADDER LESIONS		URETERAL OBSTRUCTION		PRESENT STATUS		
		SEVERE	MILD	SEVERE	MILD	LIVING	DEAD	LOST
Bladder lesions only or no lesion	7	3	3 (1 no lesion)	0	0	6	0	1
Ureteral obstruction only	6	0	0	2	4	1	2	3
Bladder lesions and ureteral obstruction	10	5	5	6	4	5	5	0
Total	23	8	8	8	8	12	7	4

Notes:
1. One living patient has recurrent carcinoma in right iliac lymph nodes after 11½ years.
2. The 4 lost patients are assumed to be dead of carcinoma.
3. Five of the dead patients are either known or assumed to be dead of carcinoma.
4. Two of the dead patients were proved by autopsy to have had no residual carcinoma (Fig. 2).
5. These two plus eleven living patients free of carcinoma make 13 patients available for the present analysis.

TABLE II. LESIONS PRESENTLY EXISTING OR EXISTING AT TIME OF DEATH IN THE THIRTEEN CASES AVAILABLE FOR PRESENT ANALYSIS

Vesicovaginal fistula	4 (2 with rectovaginal fistula)
Complete occlusion of one ureter with functionless kidney	3 (2 of these are in patients with vesicovaginal fistula)
Ureteral stricture with marked hydroureteronephrosis	2
Ureteral stricture with slight or moderate hydroureteronephrosis	4
No lesions (original mild bladder lesions only)	4

Since 1940 our standard technique for irradiation of carcinoma of the cervix has been the application of two doses of radium of 2,400 mg. hr. each with an interval of two weeks between the two applications, for a total of 4,800 mg. hr. An occasional patient has been given 4,000 mg. hr. in a single dose. For each application 100 mg. of radium element are used. A rubber tube containing two 25 mg. radium capsules in tandem is placed in the cervical canal, and a linen plaque containing 50 mg. of radium is placed against the cervix. The type and arrangement of the radium tubes in the plaque depends on the size of the cervix. The filtration has varied between 0.5 and 1.5 mm. of platinum plus 1 to 3 mm. of rubber for that in the intracervical tandem. The vagina is always packed very tightly and carefully to hold the plaque in place and to remove the bladder and rectum as far as possible from the radium. The bladder is kept constantly empty by means of a retention catheter as long as the radium is in place.

Except for the hopelessly advanced group who are treated palliatively with deep x-ray therapy only, all of the patients have received a combination of radium and roentgen irradiation. For the x-ray therapy two anterior abdominal and two posterior fields measuring 15 by 15 cm. are used. Because of danger of damage to the head of the femur we have never used lateral fields. Prior to 1941 all cases were treated at 200 KVP. At each treatment 200 r. measured in air were given over each of two fields, and the treatments were administered three times a week until a total of 8,000 r. measured with backscatter,

or 2,000 r. to each field, had been given. The factors were a skin-target distance of 50 cm., and a Thoraeus filter equivalent to 2 mm. of copper plus 1 mm. of aluminum. The half value layer was 1.9 mm. of copper.

Since 1941 most of the patients have been treated at 400 KVP., with 250 r. being administered to each of two fields three times a week until a total of 10,000 r. measured with backscatter, 2,500 r. to each of four fields, has been administered. The S. T. distance has been increased to 70 cm. and a Thoraeus filter equivalent to 3 mm. of copper plus 1 mm. of aluminum is used. The half value layer is 5 mm. of copper.

In those cases with Stages I or II carcinoma the radium is administered first and the roentgen therapy is started two weeks after the second radium treatment. In the more advanced cases the x-ray treatments are administered first and followed by radium therapy as described, if there has been a satisfactory response to the roentgen therapy.

For the sake of comparison, we wish now to present the findings on urological study of those patients treated during the years 1940 to 1942, inclusive, who survived for five years or more subsequent to their initial treatment. The absolute five-year survival rate for these three years has been 26 per cent. The results of these studies are shown in Tables III, IV, and V, and may be summarized as follows:

TABLE III. NUMBER OF PATIENTS TREATED IN 1940-1942, INCLUSIVE, WHO HAVE SURVIVED 5 YEARS OR MORE, SHOWING RESULTS OF PRETREATMENT UROLOGICAL STUDIES, AND THE LATE RECURRENCE OF CARCINOMA

STAGE OF CARCINOMA	NUMBER SURVIVING	NUMBER WITH PRETREATMENT UROLOGICAL STUDIES	CONDITION OF URINARY TRACT			LATE RECURRENCE AFTER 5 YEARS
			NORMAL	DILATATION		
				UNILAT.	BILAT.	
I	24	15	8	6	1	2
II	9	5	5			2
III	10	6	3	3		1
Total	43	26	16	9	1	5

TABLE IV. POSTTREATMENT UROLOGICAL STUDY OF PATIENTS TREATED 1940-1942, INCLUSIVE, AND SURVIVING MORE THAN 5 YEARS, WHO HAD BEEN SUBJECTED TO UROLOGICAL EXAMINATION BEFORE TREATMENT

STAGE OF CARCINOMA	CONDITION OF UPPER URINARY TRACTS BEFORE AND AFTER TREATMENT			
	NORMAL BEFORE AND AFTER	DILATATION BEFORE AND AFTER	DILATATION AFTER ONLY	NORMAL AFTER ONLY
I	3	5	0	
II	1	1	1 Late recurrence	
III	2	1		1
Total	6	7	1	1

TABLE V. POSTTREATMENT STUDY OF 7 PATIENTS TREATED IN 1940-1942, INCLUSIVE, WHO HAD NOT BEEN STUDIED UROLOGICALLY BEFORE TREATMENT

STAGE OF CARCINOMA	CONDITION OF URINARY TRACT		
	NORMAL	DILATATION	
		UNILAT.	BILAT.
I	2	2	
II	2	1	
III			
Total	4	3	0

Fig. 3. Fig. 4. Fig. 5.

Fig. 3.—E. R. (Case 240433), Stage II carcinoma. Intravenous pyelograms made Sept. 2, 1942, before the institution of treatment, showing normal upper urinary tracts.

Fig. 4.—Left retrograde pyelogram made May 9, 1947, of the same patient as illustrated in Fig. 3. Note the large hydroureteronephrosis. The left kidney was functionless and left nephroureterectomy was considered. Before this could be arranged, however, further evidence of recurrent carcinoma in the left iliac lymph nodes developed and the patient has since succumbed to carcinoma.

Fig. 5.—Right retrograde pyelogram made May 23, 1947, of the same patient illustrated in Figs. 3 and 4. There is some dilatation as compared with the pretreatment pyelograms.

Forty-one patients survived more than five years after their original treatment. Twenty-six of these were studied urologically before treatment (Table III). In 16 the urinary tracts were normal. In 10 there was evidence of slight ureteral stricture with slight hydroureteronephrosis which in all but one was unilateral. Twenty-two patients have been studied urologically since treatment, and with two exceptions these studies have been made more than five years since treatment. Fifteen of these were from the group studied before treatment (Table IV). In 13 there was no essential change in the urinary tracts between the pretreatment and posttreatment studies, six being normal and seven showing mild unilateral hydroureteronephrosis in both studies. One patient whose upper urinary tracts were normal before treatment showed a large functionless left hydronephrosis seventy-two months later (Figs. 3, 4, and 5) but has subsequently developed further evidence of a late recurrence in the left iliac lymph nodes. The ureteral obstruction in this patient was the first evidence suggesting possible recurrence. Another patient with original Stage III carcinoma and a moderate left hydroureteronephrosis now shows an essentially normal urinary tract on that side (Figs. 6 and 7).

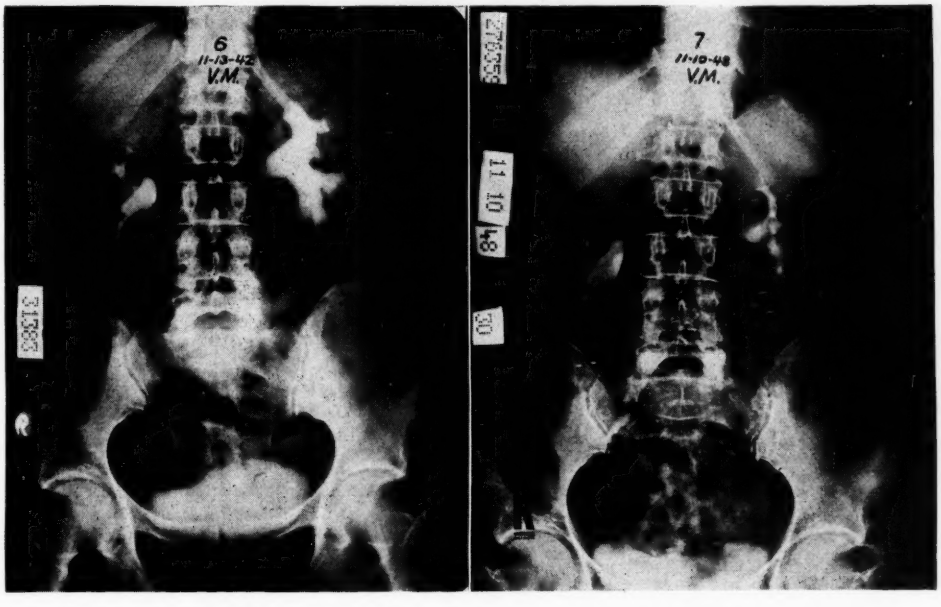

Fig. 6. Fig. 7.

Fig. 6.—V. M. (Case 276359), Stage III carcinoma. Pretreatment intravenous pyelogram Nov. 13, 1942, showing moderate left hydronephrosis.

Fig. 7.—Intravenous pyelogram Nov. 10, 1948, of the same patient illustrated in Fig. 6. The patient has been clinically well of carcinoma for more than six years, and there has been complete regression of the left hydronephrosis.

Seven of the patients studied subsequent to treatment had not been subjected to pretreatment studies (Table V). In four of these the urinary tracts are normal. In one there is slight right hydronephrosis. In one with a late recurrence in the right iliac lymph nodes there is a functionless right kidney. The third patient has a large right hydronephrosis which has progressed since it was first discovered eight months after treatment, but which is apparently due to ureteropelvic junction obstruction and therefore is not related to the carcinoma or its treatment (Figs. 8 and 9).

No bladder ulcerations or vesicovaginal fistulas have *as yet* occurred in any of these patients. We say *as yet* because, even though six to eight years have elapsed since treatment in all of them, we have seen such bladder lesions develop as late as twelve years subsequent to treatment. Of the total group of 149 patients treated in the three years under consideration, 10, or 6 per cent, developed vesicovaginal fistulas. None of these 10, however, survived as long as five years, and all of them are assumed to have died of carcinoma.

In this group, then, we have found no urological lesions that can be conclusively attributed to irradiation therapy. We must conclude, therefore, that the technique and methods of administration of the irradiation therapy used during the years under consideration were far superior to those previously used in so far as the prevention of postirradiation urological complications is concerned.

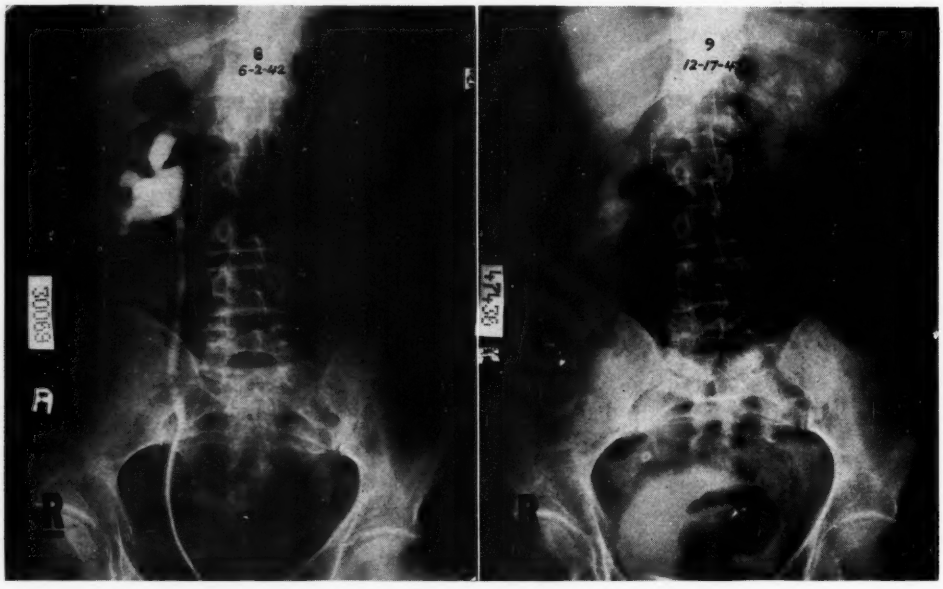

Fig. 8. Fig. 9.

Fig. 8.—A. M. (Case 234772), Stage I carcinoma. Right pyelogram June 2, 1942, eight months after treatment showing hydronephrosis apparently due to ureteropelvic junction obstruction.

Fig. 9.—Intravenous pyelogram Dec. 17, 1947, of the same patient illustrated in Fig. 8. There has been progression of the hydronephrosis, but it is producing no symptoms and the patient is apparently well of carcinoma. Obstruction in this region could hardly result either from the carcinoma or its treatment.

During the war years due to shortage of personnel and more particularly to the frequent almost complete unavailability of x-ray films for use except in the most urgent cases, the routine urological study of cases with cervical carcinoma was discontinued. The patients treated, therefore, during those years will never be available for accurate statistical analysis as regards urological damage. Since the war, however, the routine urological studies have been resumed, but sufficient time has not elapsed to permit a study of these patients to be of any statistical value.

Since 1945 we have treated a small series of 39 cases with somewhat larger doses of radium. This second technique differs from the one described above in that the lower 25 mg. tube in the intracervical tandem is replaced by

a 50 mg. tube, making a total of 75 mg. of radium applied to the cervical canal. The same type of 50 mg. contracervical plaques described above are used, so that, in all, 125 mg. of radium are applied for two applications of 3,000 mg. hr. each. The filtration has varied between 0.5 and 1.5 mm. of platinum, plus 1 to 3 mm. of rubber in the case of the intracervical tandem. The x-ray dosage and technique in this group have been the same as that described for the former group after 1941, that is, a total of 10,000 r. measured with backscatter, administered from a 400 KVP machine. The isodose curves for this technique are shown in Fig. 10, and may be compared with those for the original technique of 4,800 mg. hr. of radium and 8,000 r. of x-ray from a 200 KVP machine shown in Fig. 11.

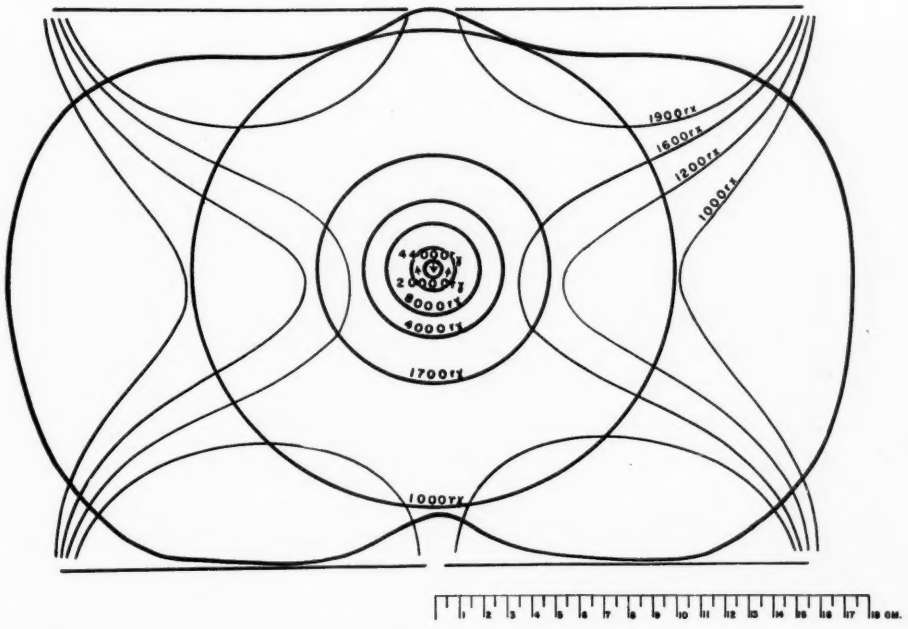

Fig. 10.—Shows the distribution of intensity of irradiation from x-ray and radium for the following conditions: The x-rays are delivered in 250 r. doses measured with backscatter through two posterior and two anterior pelvic fields 15 by 15 cm., each field receiving a total of 2,500 r. The factors are 400 KVP., 70 cm. skin-target distance, Thoraeus filter equivalent to 3 mm. of copper plus 1 mm. of aluminum. The radium is administered in one intracervical tandem preparation and one contracervical plaque. The former contains one 25 mg. and one 50 mg. radium capsule with a wall thickness of 0.5 mm. of platinum and 3 mm. of rubber. The plaque consists of five 10 mg. tubes with a wall thicknes of 0.5 mm. of platinum. Two applications are administered, each consisting of 1,800 mg. hr. of intracervical and 1,200 mg. hr. of contracervical radiation. This is the technique which was used in the thirty-nine patients who showed a high percentage of severe irradiation reactions.

In both this chart and Fig. 11 the intensity of radium irradiation is shown by the heavier concentric circles, and that of x-rays by the lighter curves. The intensity of radium irradiation is expressed in rγ, and the depth doses from x-radiation, expressed in r_x1, represent percentage values derived from the total dosage, which are expressed in r. measured in air.

In the group of cases treated with the smaller radium dosage (4,800 mg. hr.), the incidence of radiation necrosis of the cervix severe enough to cause apprehension has been approximately 4 per cent of the cases treated. In the 39 cases treated with 6,000 mg. hr. of radium, 12 cases showed moderate to severe radiation necrosis of the cervix or other reaction such as induration in the parametrium or cul-de-sac, an incidence of 31 per cent. Thus an increase in the total radium dosage from 4,800 to 6,000 mg. hr. resulted in an increase in pelvic irradiation reactions from 4 to 31 per cent, with two deaths which

could be attributed at least partly to the radiation therapy. It is felt that the majority of these patients showing radiation reaction at the present time will evenually have a good postradiation result, it being too soon after treatment to be sure of the final response to therapy. However, two of these patients, including one of those who died, sustained severe damage to the urinary tract, which we feel should be mentioned in this report.

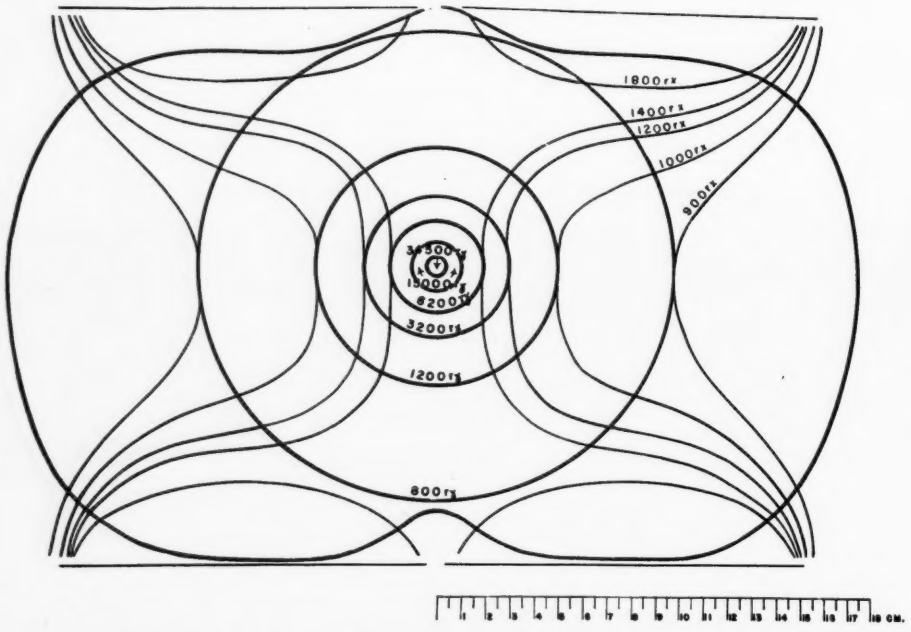

Fig. 11.—Shows the distribution of intensity of irradiation from x-ray and radium for the following conditions: The x-rays are delivered in 200 r. doses measured in air through two posterior and two anterior pelvic fields 15 by 15 cm., each field receiving a total of 2,000 r. The factors are 200 KVP., 50 cm. skin-target distance, Thoraeus filter equivalent to 2 mm. of copper plus 1 mm. of aluminum. The radium is administered in one intracervical tandem preparation and one contracervical plaque. The first contains two 25 mg. tubes with a wall thickness of 1 mm. of platinum and 3 mm. of rubber. The second consists of five 10 mg. tubes with a wall thickness of 0.5 mm. of platinum. Two applications are administered, each consisting of 1,200 mg. hr. of intracervical and 1,200 mg. hr. of contracervical radiation.

This is the technique used in 1940 and the earlier part of 1941. Later in 1941 and in 1942 the radium technique was the same but the x-ray dosage was that shown in Fig. 10. The five-year survivors among the patients treated in these years have shown no urological damage attributable to irradiation.

CASE 1.—A 25-year-old Negro, para ii, complained of periodic intermenstrual bleeding of one year's duration. One month before coming to the clinic she bled continuously for ten days. Lower abdominal pain had been present for five months. Examination revealed a deeply lacerated cervix with a hypertrophied anterior lip, and a granular lesion measuring 2 cm. on the left side of the cervix. The fundus was normal and was free, but there was induration in the medial part of the left parametrium. A biopsy was reported "Epidermoid Carcinoma of the Cervix, Transitional Cell Type," and a diagnosis of carcinoma of the cervix, clinical Stage II was made. The patient was given two radium treatments of 3,000 mg. hr. each at two-week intervals, and this was followed by the usual course of 10,000 r. of deep x-ray therapy at 400 KVP. Five months after treatment was started a small ulcer was noted on the cervix, and the parametrium on both sides were found to be quite indurated. A month later she developed persistent rectal bleeding and anemia requiring blood transfusions, and eight months after treatment was started she was found to have a rectovaginal fistula. In order to put the bowel at rest a colostomy was done

but the patient continued to bleed profusely. An attempt was made to ligate the hypogastric arteries but because of the adhesions and induration in the pelvis, they could not be isolated. An intravenous pyelogram at this time revealed a functionless right kidney, and on cystoscopic examination a No. 6 ureteral catheter would pass for only 2 cm. up the right ureter. The patient died suddenly the next day after an exsanguinating hemorrhage. Autopsy revealed massive induration and fixation of all the pelvic structures. There was a large rectovaginal fistula, and in the right parametrial region was an irregular cavity measuring 4 cm. in diameter. A segment of the right ureter the length of the cavity was completely destroyed, so that the remaining upper and lower portions of the ureter communicated with the cavity (Fig. 12). Numerous microscopic sections from the pelvic organs failed to reveal any persistent carcinoma cells. This case is undoubtedly one of rectovaginal fistula, destruction of the ureter with functionless kidney, and death resulting from irradiation therapy.

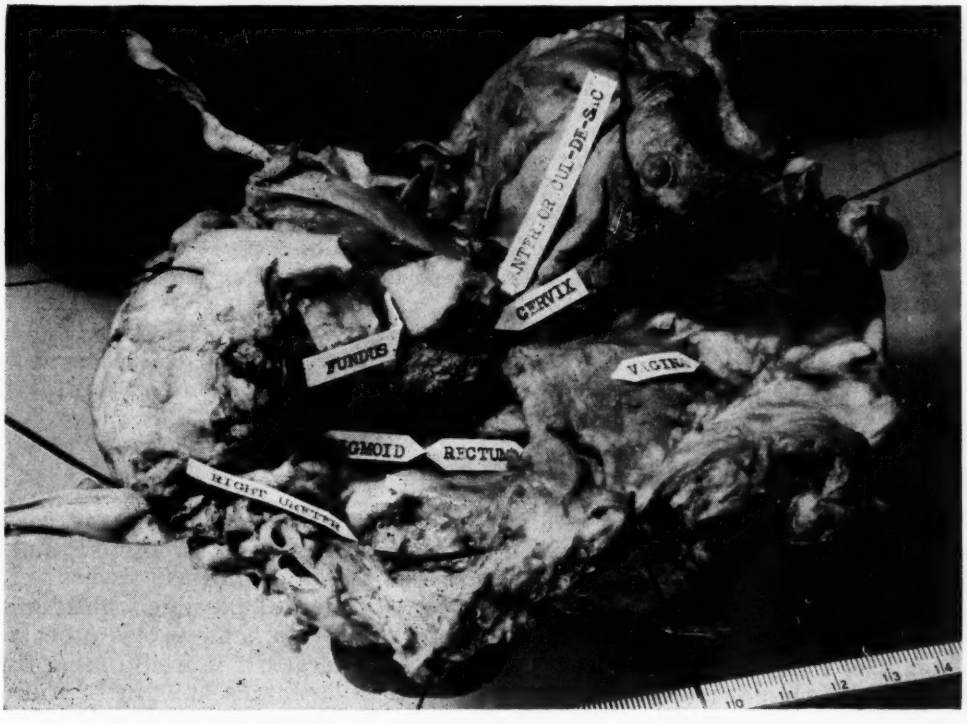

Fig. 12.—Autopsy specimen from a patient dying of hemorrhage from the bowel nine months following irradiation treatment (6,000 mg. hr. of radium and 10,000 r. of deep x-ray therapy at 400 KVP.) for Stage II carcinoma of the cervix. Note the necrotic cavitation in the right broad ligament region and complete destruction of a segment of ureter in the same region. There was also a large rectovaginal fistula. No remaining carcinoma was found in the sections.

CASE 2.—Our second recent case of severe damage to the urinary tract is that of a 38-year-old Negro para iii with an old history of right pulmonary tuberculosis for which she had had the right lung collapsed by pneumothorax for six years. There was also a history of essential hypertension. She was seen in January, 1947, complaining of menorrhagia, and was examined many times between January and October of the same year. During this period a total of four biopsies was taken, the first and last of these showing intraepithelial carcinoma. In October, pelvic examination revealed a cervix which was covered with normal-looking mucosa. The fundus was on the upper border of normal in size and both adnexa were normal. Although it is customary in our clinic to treat noninvasive carcinoma of the cervix by means of the modified Wertheim operation, it was

felt in this case that surgery was contraindicated because of the medical complications, and irradiation therapy was used in its place.

On Oct. 28, 1947, a sharp conization of the cervix was done in order to supply additional tissue for microscopic examination. Study of this tissue revealed an early invasive carcinoma of the cervix, of basal-cell type. Immediately after the conization the patient was given 1,837 mg. hr. of intracervical radium therapy with one 25 and one 50 mg. radium capsule in tandem in a rubber cot. Next day 1,225 mg. hr. were given contracervically, and two weeks later 1,800 mg. hr. were given intracervically and 1,200 contracervically using the same technique. Between Dec. 2, 1947, and Jan. 28, 1948, the patient was given a total of 10,000 r. of deep x-ray therapy over four pelvic portals. The patient was well for six weeks when she returned complaining of abdominal pain on urination, and pelvic examination revealed induration and fixation in the left parametrium. Three months after treatment was completed she had a sudden profuse vaginal hemorrhage and was admitted to the hospital. On examination there was a large irradiation ulcer replacing the cervix, and a large vesicovaginal fistula measuring 3 to 4 cm. in diameter. Profuse bleeding continued from the edges of the ulcer in spite of continued packing with Gelfoam gauze, and it was finally necessary to ligate the anterior branches of both hypogastric arteries in order to control the hemorrhage. It was discovered at operation that there was a moderate right hydroureter, and the right ureter was transplanted to the sigmoid colon to preserve the function of the right kidney. Since operation the patient has done well except for an episode of vaginal bleeding from the border of the vesicovaginal fistula in October, 1948. It has been decided to transplant the left ureter to the colon eventually, but this procedure has been postponed because it is feared that the anesthesia may influence adversely the course of the pulmonary tuberculosis, which is doing well at the present time.

We feel that the extensive damage to the urinary tract as well as to some of the other pelvic structures in this case is due as much to the fact that radium was applied immediately after the conization of the cervix as to the large dose of radium that was used. We have since discontinued both of these procedures.

Comment

The main objective of irradiation therapy of carcinoma of the cervix should be, and no doubt is, to obtain as high a salvage rate as possible, and at the same time to avoid inflicting serious damage upon normal tissues. The purpose of a study of this type is to try to determine if possible what factors of technique of irradiation therapy are most likely to achieve this objective. From this study and others gathered from the literature, it would seem that, of the two components of the treatment, variation in the amount of radium irradiation administered, and more especially in the time required to administer it, is of more importance than variations in the x-ray therapy, provided excessive x-ray dosage is avoided. In the earlier series, many of the patients who developed severe urinary tract damage had received no x-ray therapy, and several of them had received less than 3,000 mc. hr. of radon. However, in all of them the radon had been administered rapidly without anesthesia, and therefore without the possibility of as careful packing of the vagina as can be accomplished in the anesthetized patient.

In our second series of patients who received 4,800 mg. hr. of radium and 8,000 to 10,000 r. of x-ray there was no urinary tract damage in the patients who survived five years or more, but the radium was administered by two 24-hour applications of 100 mg. of radium with an interval of two weeks between treatments. In our third small series of patients who received the same x-ray dosage, but in whom the radium dosage was increased to 6,000 mg. hr. by increasing the amount of radium by 25 per cent, but leaving the time

required for administration the same, there has been a high percentage (31 per cent) of severe postirradiation reactions.

At the University of Maryland Hospital from which Diehl and Hundley have reported no demonstrable evidence of urinary tract damage, and where the technique of radium application was very similar to ours, 6,000 mg. hr. of radium are routinely given. However, only 100 mg. were used for two applications of 30 hours each with an interval of three weeks between the two. This was followed by 6,000 to 8,000 r. of x-ray which was repeated after twelve weeks. In a recent article, Kimbrough and Muckle have reported the results of their technique at the Pennsylvania Hospital which also consists of the administration of 6,000 mg. hr. of radium, using only 60 mg. of the element which is left in place for 100 hours either as a single application or as two applications a month apart. Their x-ray dosage is small, 2,000 to 2,800 r. They have encountered a negligible amount of postirradiation reaction.

Morton and Kerner have recently described the technique used at the University of California. Two radium applications are administered two weeks apart. The first of these consists of 150 mg. (three 50 mg. capsules) within the cervix for a total of 3,000 mg. hr. At the second treatment 100 to 150 mg. of radium are applied against the cervix for a total of 1,500 mg. hr. Their standard x-ray dosage is 12,000 r., 3,000 r. to four pelvic fields using either a 200 or a 1,000 kv. machine. These authors have reported on all types of reactions which apparently have been considerably more frequent than have been noted by others using smaller quantities of radium over longer periods of time.

Conclusions

From the study here reported we believe that the following conclusions are justified:

1. The urological study of patients before and at repeated intervals subsequent to treatment of carcinoma of the cervix by irradiation therapy is a valuable procedure.

2. Such studies aid in the estimation of prognosis, the determination of response to treatment, the early detection of late recurrence of the cancer, and the detection of urinary tract damage resulting from the treatment.

3. The early detection of such irradiation damage to the urinary tract makes possible appropriate treatment before ureteral obstruction has advanced to such a degree as to endanger the life of the patient.

4. Radium is potentially more dangerous than x-ray therapy in so far as the production of urinary tract damage is concerned.

5. The potential danger to the urinary tract and other normal structures from radium irradiation is reduced by achieving the desired milligram hour dosage with smaller amounts of radium administered over longer periods of time.

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Discussion

DR. JOHN B. MONTGOMERY, Philadelphia, Pa. (by invitation).—Dr. Everett's three groups of carefully studied patients show clearly the accidental effect of various plans of irradiation therapy of carcinoma of the cervix upon the urinary tract and surrounding tissues and also demonstrate the value of repeated urologic studies in the management of this lesion. In his first group of patients comparatively small amounts of irradiation with radium administered quickly resulted in a rather high incidence of urinary tract and local tissue damage. On the other hand, larger amounts of irradiation administered less rapidly in conjunction with x-ray therapy have provided adequate treatment in the second group with practically no urinary tract damage that could be attributed to the irradiation. In Dr. Everett's third group of patients, it is interesting to note that, in the presence of roentgen therapy, administered as 2,500 r. to each of four portals, increasing the radium dosage from 4,800 mg. hr. to 6,000 mg. hr., or apparently by only 25 per cent, resulted in a tremendous increase in severe local tissue reactions. This increase was accomplished by adding 25 mg. of radium to the lower half of the 50 mg. tandem application to the cervical canal, thereby actually doubling the dose in the area that was already receiving the most intense irradiation by virtue of the cross fire from the 50 mg. plaque placed against the cervix. This is shown graphically in the isodose curves that Dr. Everett has prepared but has not had time to present. The resulting high intensity irradiation applied to a small area probably was the main factor in producing the severe local reaction. Dr. Everett's present plan of administering deep roentgen therapy (2,500 r. to each of four portals) followed or preceded by the application of 4,800 mg. hr. of radium in two doses of 2,400 mg. hr. each at two-week intervals has proved to be far superior. This plan is similar to that in use on the Division of Gynecology in The Jefferson Medical College Hospital, except that we apply 3,600 mg. hr. of radium at one sitting beginning three to four weeks *after* completion of roentgen therapy.

Since 1942, we have endeavored to increase this amount of irradiation to the cervix without damaging the bladder by supplementing the external irradiation (2,000 r. to four portals) prior to the local radium application (3,600 to 4,000 mg. hr., intracavitary and interstitial) by transvaginal roentgen therapy (2,000 to 2,500 r.). The incidence of local tissue injury, following this plan, has not yet been evaluated but it is our impression that, although there may be some increase in bowel irritation of moderate degree, there has been no increase in injuries to the urinary tract.

This experience of Dr. Everett in applying increasing amounts of irradiation to the cervix in the hope of accomplishing more complete destruction of the tumor no doubt has been shared by many of us. It is often difficult for the gynecologist, who bears heavy responsibility in treating these unfortunate women, to realize that there is an optimum irradiation dose beyond which even comparatively small increases may be harmful. On the other hand, some individuals are unusually susceptible to irradiation therapy and may suffer severe tissue damage from a dose that is well tolerated by others. This was clearly illustrated by two of our patients who were treated in June and July, 1939. Both were moderately obese white women. One was 51, the other 44 years of age. Each had a squamous-cell carcinoma of the cervix of approximately the same extent, Stage II or early Stage III, Schmitz. Six weeks after the administration of deep x-ray therapy in the form of 2,000 r. to each of four portals radium was applied according to our usual plan. One 50 mg. capsule screened with 1.5 mm. of platinum was inserted into the cervical canal and ten 10 mg. needles screened with 0.5 mm. of platinum were inserted around the periphery. The usual application of 3,600 mg. hr. was increased to 4,500 mg. hr. One patient developed slight local necrosis and mild bladder symptoms but recovered and is now well and apparently free of disease. The other patient developed extensive local necrosis and died of sepsis seven months after treatment. Autopsy revealed extensive necrosis of all pelvic tissues but no evidence of carcinoma.

The value of repeated urologic study is shown most clearly by Dr. Everett in the group of patients who were treated with high-intensity radium therapy prior to 1939.

These studies revealed not only a relatively high incidence of urinary tract obstruction in patients so treated but they have shown that these injuries have persisted and in some instances have progressed in the small group of patients who have survived and who apparently are free of malignancy. The importance of the early recognition and careful repeated follow-up study of such lesions cannot be overemphasized. As Dr. Everett suggests, they are probably due to progressive irradiation fibrosis, yet in occasional instances obstruction of the ureter has been the first sign of recurrence of the carcinoma.

In those patients treated from 1940 to 1942 with roentgentherapy and a less intense application of radium, repeated urologic examination revealed no instance of urinary tract damage attributable to irradiation. This is an enviable record and it is undoubtedly influenced by the care and skill with which the treatment was carried out as well as to the reduction in the intensity of the irradiation. It is of interest to note in this group that coincidental urethral obstruction present before treatment in seven of fifteen patients with Stage I carcinoma was not influenced unfavorably by the irradiation therapy.

Our experience with irradiation therapy in carcinoma of the cervix in general has been similar to that of Dr. Everett. The recent figures presented by Dr. Scheffey before the Medical Society of the State of Pennsylvania in September, 1948, show a relative five-year survival of 38 per cent in patients treated from 1936 to 1943. In 116 patients with all stages of carcinoma studied by intravenous urography, following therapy, between Sept. 1, 1943, and Sept. 1, 1945, we found urinary tract obstruction in 62, or 53.4 per cent. Approximately 25 per cent of the patients who had originally Stage I and Stage II lesions showed some evidence of ureteral obstruction. All were of mild degree except one which was proved later to be due to an extension of the disease. More than 50 per cent of Stage III patients and a somewhat greater percentage of those with more advanced lesions were found to have obstructions that were considered to be of clinical significance. In the small group of our patients who have had urologic studies both before and after treatment, we have noted, as has Dr. Everett, that ureteral obstruction before treatment in Stage III patients was a grave prognostic sign, all such patients having died within one year.

The importance of persistent upper urinary tract damage in patients who have responded satisfactorily to irradiation therapy is illustrated by one patient who was treated for Stage III carcinoma by our usual planned technique in March, 1941. Her convalescence was uneventful but she continued to have moderate induration in the right parametrium. In March, 1942, one year after completion of her treatment, she was readmitted in critical condition with abdominal pain, distention, and vomiting. The admitting diagnosis was extensive recurrent carcinoma of the cervix with peritontis. Further study revealed extensive urinary tract infection with complete obstruction of the right ureter and right hydronephrosis. After removel of the kidney, the patient recovered completely and is now living and apparently free of malignancy.

Incidents such as this, which have occurred not infrequently in our experience, together with the results of Dr. Everett's carefully repeated studies, have convinced us that urinary tract studies before treatment and at intervals thereafter may be of considerable importance in the management of the patient with cervical cancer.

DR. C. BERNARD BRACK, Baltimore, Md. (by invitation).—As. Dr. Everett has stated, we are convinced that intensity is the most important single factor in producing urinary tract damage. However, in our last series of cases where there was an increase in the incidence of urinary tract complications, we increased the quantity of radium dosage to the cervix and to the paracervical tissues as well as increasing the intensity of the irradiation. This is illustrated by Fig. 11 in Dr. Everett's paper, which shows the intensity of the irradiation with our original technique. The dosage was very high—34,500 r. delivered to the tissues at the center of the cervix. However, with this technique, we had little urinary tract damage. The incidence of vesicovaginal fistula was 6 per cent. The incidence of all complications was 11 per cent and did not exceed 17 per cent in any one year. The corrected five-year salvage over a three-year period was 26 per cent and in one year was almost 33 per cent.

Fig. 10 shows the distribution of irradiation to the pelvis when the larger irradiation dose, 6,000 mg. hr., was used in conjunction with 400 kv. x-ray therapy. The dosage to the cervix is quite high and it is not surprising that we ran into a high incidence of irradiation reactions with this technique. As Dr. Everett has stated, the incidence of reactions of all types is 31 per cent and there was severe ureteral damage in at least 5 per cent. Since these patients were all treated since the war, we do not know yet what the five-year salvage will be but we think it will be respectible in spite of the high incidence of irradiation reactions. Needless to say, we have discontinued this last technique and are now using 4,800 mg. hr. total radium dosage, in conjunction with 400 kv. x-ray delivered over four external portals, and in addition we are using a vaginal cone angled toward the fornices, in an attempt to deliver additional irradiation to the parametrium. Dr. Everett and I plan to continue this study and should have another report ready in another 10 years.

DR. J. MASON HUNDLEY, JR., Baltimore, Md.—Wishing to learn if radiation of the malignant cervix produced changes in the ureteral wall, we began a study* of this problem in 1937. A group of 37 patients with carcinoma of the cervix was selected for complete urological studies. Of these, 11 were in Grade I and 2 of these showed dilatation of the tract before therapy; 9 were in Grade II and 1 showed dilatation of the tract before therapy; 17 were in Grade III and 7 of these showed dilatation of the tract before therapy.

The patients were then given radium application in broken doses, 3,000 mg. hr. in two treatments three weeks apart, making a total of 6,000 mg. hr. This was followed in three weeks by a cycle of deep x-ray therapy of 7,000 r. Twelve weeks later another cycle of 7,000 r. was given

One year later another urographic study was carried out and the following results were noted: No patients in Grades I and II showed development of dilatation. In Grade III, 7 patients originally showed dilatation; 6 of these showed no appreciable change between the two urographic studies, and the remaining patient showed increasing dilatation and eventual death from carcinoma. Of the remaining 10 patients, 4 developed dilatation, 3 of them dying with carcinoma and associated marked urinary tract dilatation in less than two and one-half years. The one remaining patient with minimal dilatation lived seven years and three months and died of carcinoma.

Believing that urinary tract changes, i.e., hydroureter and hydronephrosis, might possibly develop at still a later date, another urographic study was carried on by the intravenous method more than nine years later. Results of this third intravenous urographic study made on the twenty survivors follows: One urogram made twelve years after the original study showed slight increase in degree of dilatation; the remaining patients studied showed either normal urograms or no increase in the pre-existing pathology.

Of the original 37 patients investigated at the onset, the survival rate is now as follows:

One patient was lost track of, having moved to New England after 1946, but at that time she was doing well, six years after her first visit.

Over-all survival, 5 years, 70.2 per cent.

Over-all survival, 8 years, 54.0 per cent.

Important factors to be considered for good results are: (1) small amount of radium with heavy filtration; (2) prolonged radiation; (3) proper application of pack, and (4) maximal vaginal packing. The proper packing of the vagina is of importance for it occasions considerable displacement of the focal point so that the ureter reecives a minimum of radiation.

In conclusion, we believe, from our studies, that radiation of the malignant cervix plays a minimal role, if any, in the production of dilatation changes in the urinary tract.

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*Note: This article with the exception of the third urographic study appears in Surg., Gynec. and Obst. for December, 1948.

DR. EVERETT (Closing).—Our objectives in these studies are to determine the best method of irradiation to acquire the highest salvage rate and at the same time avoid destruction of normal tissues. I would have been very much interested if Dr. McKelvey had mentioned complications in his studies. From our study I would think his complications would be very low because he uses very small doses of radium over a long period of time, and our studies would seem to indicate that that is the answer.

Dr. Hundley is fortunate in not having had many urologic complications, but he has given the radium slowly. I believe that we have proved that if you step up the speed with which you give irradiation you get complications. We have worked on this for nearly twenty years. Our results have improved and in another ten years I hope to be able to bring in a report with a salvage rate equaling Dr. McKelvey's and with no urologic complications.

THE LYMPHATIC SPREAD OF CARCINOMA OF THE CERVIX AND OF THE BODY OF THE UTERUS*

A Study of 420 Necropsies

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THE revival of interest in the surgical treatment of carcinoma of the cervix[6, 8, 33, 34, 36, 46, 48] emphasizes the need for further study of this disease on an anatomical and pathological basis. Unfortunately, there is no exact means of determining the true extent of the clinical spread of the cancerous growth, except by necropsy. The study of necropsy material has its limitations, but it does permit a thorough examination of the ravages of the malignant disease and a correlation of the pertinent findings between the treated and the nontreated cases.

The Material

The 420 cases in this series include 64 cases of adenocarcinoma of the corpus uteri, and 356 cases of carcinoma of the cervix. The cervical series also includes adenocarcinomas of the cervix (fourteen cases) and in addition, carcinoma of the cervical stump (thirty-two cases). The series is further divided into the treated and the nontreated groups. "Treatment" consisted of radiation therapy, and, in most instances, included x-ray and radium.

The classification of the League of Nations[27] has been followed in classifying the clinically determinable extent of the cervical carcinoma. The nontreated cases are classified according to the clinical interpretation of the extent of the disease at the time of the patient's last admission to the hospital.

The clinical classification of the treated case was established at the time of the first treatment. It is well known that the clinical estimation of the extent of the disease is imperfect and this is substantiated in our study by an error of over 25 per cent when the clinical estimate is compared with the findings at necropsy. In most instances, inflammatory induration of the parametrium was misinterpreted as clinical evidence of malignant extension.

Careful lymph node dissections were done on twenty-six nontreated and fifteen treated cases of carcinoma of the cervix and ten cases of corporeal adenocarcinoma. In each case the nodes were properly segregated, and in addition one block was taken through each parametrium. An average of four sections was made of each block, serial sections being impractical.[26, 41, 42] Obviously this less complete method of examination will overlook some metastases. Therefore the figures presented in this study may not represent the actual incidence of metastases.

The Lymphatics of the Cervix (Fig. 1)

The pathways of the lymphatic vessels and the anatomical sites of the nodes have been carefully studied by many observers.[11, 22, 39, 40, 43, 45] From our observations it is permissible, we believe, to separate the lymphatic nodes into primary and secondary groups.

*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

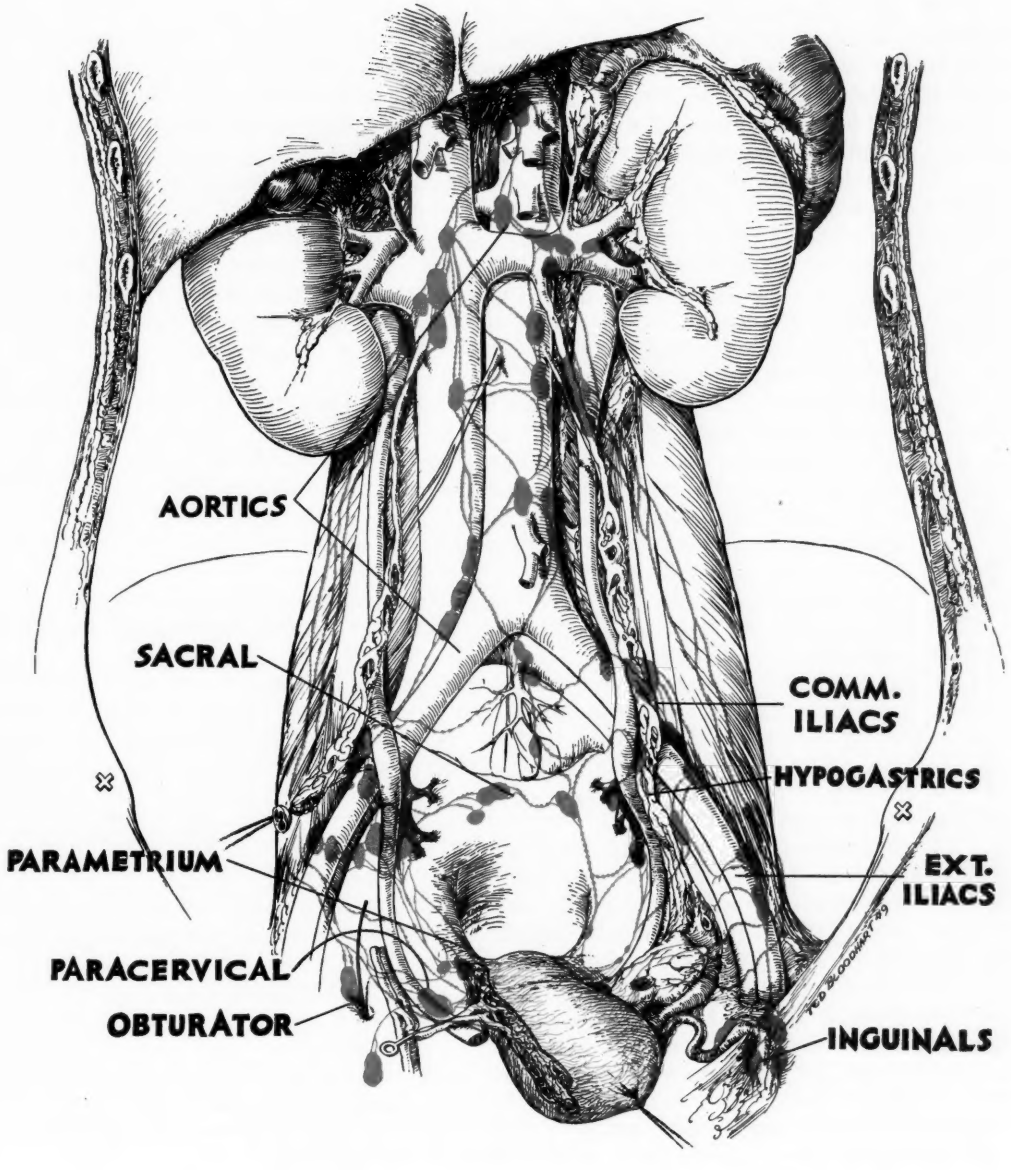

Fig. 1.—Lymph vessels and lymph nodes of the cervix and the body of the uterus.

I. *The Primary Group.*—

A. *The Parametrium:* The presence of small lymph nodes along the major lymphatic trunks traversing the parametrium is constant enough to permit their inclusion as a separate chain of lymph nodes.

B. *The Paracervical (Ureteral) Node:* Located near the crossing of the uterine artery and the ureter, this node was not recognizable in 8 per cent of the treated cases and in 3 per cent of our nontreated cases of cervical carcinoma.

C. *The Hypogastric Nodes:* The uniformly small nodes in this group vary in number and location, and are located along the course of the hypogastric vein, near its junction with the external iliac vein.

D. *The Obturator Nodes:* These are frequently described as one large node (Leveuf's node[28]). We have found as many as three distinct nodes, associated with the obturator vessels and nerve, near the obturator foramen.

E. *The External Iliac Nodes:* This group varies in number from three to eight nodes, which tend to be uniformly larger than the nodes of the other groups. Usually located in the sulcus between the external iliac artery and vein, they may be found entirely on the mesial surface of the vein.

II. *The Secondary Group.*—

A. *The Sacral Nodes:* This group includes the several nodes in the sacral concavity and on the sacral promontory.

B. *The Common Iliac Nodes:* These vary in number and location, but usually lie on the mesial and lateral surfaces of the common iliac vessels, just below the bifurcation of the aorta.

C. *The Inguinal Nodes:* These include the deep and superficial femoral lymph nodes.

D. *The Aortic (Periaortic) Nodes:* These extend from the level of the bifurcation of the aorta to the diaphragm, and they lie on the superior and the lateral aspects of the aorta.

The lymph channels and node sites are often variable due to the ever-present intercommunicating subsidiary vessels and the relatively inconstant locations, exhibited by some of the major nodes. It was also not uncommon to find anomalous nodes along the lymph vessels connecting the major node groups. These intercommunicating vessels account for the unpredictable sites of some of the metastases.

The lymphatic vessels draining the cervix converge at the level of the junction of the cervix and the corpus to form the paracervical plexus, from which main trunks pass laterally, and follow the direction of the uterine veins. Between these main trunks are intercommunicating vessels, which permit the occasional by-passing of a major node group located along the main lymphatic route.*

Channel 1: Arising from the paracervical plexus and following the direction of the uterine artery, this channel connects with the paracervical, the external iliac, and the obturator nodes.

Channel 2: This channel also arises from the paracervical plexus, follows the course of the uterine vein posteriorly, to terminate in the hypogastric nodes. Intercommunicating vessels permit frequent metastases between the hypogastric, the obturator, the external iliac, and the sacral node groups.

Channel 3: This is a smaller and less constant channel which passes forward and then backward along the uterosacral folds on both sides of the rectum, to terminate in the sacral nodes located in the concavity and on the promontory of the sacrum. Though this node group is included as a part of the secondary group of nodes, intercommunicating channels frequently permit metastases to the hypogastric nodes, before the sacral nodes are involved. These subsidiary channels are so constant that it is permissible to interpret them as major routes.

*Injection of "Pantomine Sky-blue" (E. I. du Pont de Nemours & Co., Inc.) into the cervix prior to laparotomy frequently permits an easy tracing of the lymph channels and the localizing of the nodes.

The Lymph Nodes[36, 46, 47, 51]

It is difficult to interpret correctly the pathological status of a node either at operation or necropsy. Enlargement of a node is not pathognomonic of metastasis. Alteration in size may be due to an inflammatory process while a small adjacent node may contain carcinoma. As a rule, however, large adherent or necrotic nodes are malignant. In this study, the error of our ability to estimate properly the presence or absence of cancer from the gross appearance of the node at necropsy was approximately 20 per cent.

Normal lymph nodes vary not only in size and histological structure in different individuals, but such variations may be readily noted in the same individual. It is not uncommon to find enlarged, but histologically normal nodes in close proximity to nodes containing cancerous cells. In this series no constant histological changes in the nodes attributable to the effect of irradiation were found. The marked fibrosis and hyalinization usually interpreted as an indication of the effects of prolonged and intensive irradiation were also present in some of the nodes from the nontreated cases. Evidence of node disintegration is more common in the treated cases. The nodes of 17 per cent of this group, located within the accepted range of the effect of irradiation, exhibited no disturbance of their histological patterns. On the other hand, over 12 per cent of the nontreated cases had nodes which showed the changes generally attributed to the effects of irradiation. It has been impossible, from our observations, to determine the amount of irradiation by the changes within the node. Minute islands of malignant cells are occasionally found within a thickened, fibrous and hyalinized node, but we are not prepared to correlate, however, the effect of irradiation upon the metastasis. Some of these malignant inclusions appear so completely encapsulated as to prevent further growth, but it is also probable that their growth is only temporarily restrained. In 4 per cent of the treated and 7 per cent of the nontreated cases, we found small glandular inclusions interpreted by some as probable islands of endometrial glands.

Part I

The careful dissection of the lymph nodes and parametria in forty-one cases at necropsy offered a fairly consistent pattern of carcinomatous dissemination in carcinoma of the cervix. The size of the series does not permit the indexing of the nodes according to their order of involvement, but it is apparent that one or both parametria, and one or more nodes of the primary group, are usually involved before metastases extend to nodes of the secondary group. This material is set forth briefly.

A. *Carcinoma, Cervix Uteri,* twenty-six nontreated cases (Table I).—

Clinical Stage I, five cases: These patients died of conditions unrelated to the cervical growth. Though there was no parametrial induration, unilateral involvement of the paracervical node was present in two cases. Three of the patients had non-neoplastic induration of the parametria with nonmalignant enlargement of the primary group of nodes.

Clinical Stage II, six cases: Unilateral involvement of the parametrium occurred in five of the six cases, while associated inflammatory-type induration of the parametrium occurred in four of the cases. Two of the cases had a total of seven metastatic nodes, including nodes of the secondary group. Eleven nodes showed an inflammatory enlargement. Three of this group died of causes unrelated to the malignant growth; two died from operative shock following attempted radical surgery; one died of uremia secondary to unilateral malignant induration of the parametrium.

Clinical Stage III, eight cases: Bilateral involvement of the parametrium occurred in seven of the eight cases. Five of these cases exhibited small meta-

static deposits in the parametrium. There was a total of thirteen primary and seven secondary group node metastases and one distant metastasis. That lymphatic extension does not occur at a constant rate is supported by the fact that unilateral node involvement is not uncommon where the parametria are equally involved.

Clinical Stage IV, seven cases: Bilateral involvement of the parametrium in six of the cases. Twenty primary group nodes, nine secondary group nodes, and six distant metastases were present in this group.

TABLE I. INCIDENCE OF NODE GROUP INVOLVEMENT IN TWENTY-SIX NONTREATED CASES OF CERVICAL CARCINOMA

	Parametrium		Paracervicals		Obturators		Hypogastric		Ext. Iliacs		Com. Iliacs		Inguinals		Sacral	Aortics	Dist. metas.
	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT			
STAGE I (5)	–	–	2	–	–	–	–	–	–	–	–	–	–	–	–	–	–
STAGE II (6)	3	2	2	1	–	2	1	–	1	–	–	–	–	–	1	1	–
STAGE III (8)	8	7	3	3	4	3	1	2	3	1	3	–	1	1	1	2	1
STAGE IV (7)	7	6	3	2	5	3	4	5	3	2	5	1	–	–	4	4	6

TABLE II. INCIDENCE OF NODE GROUP INVOLVEMENT IN FIFTEEN TREATED CASES OF CERVICAL CARCINOMA

	Parametrium		Paracervicals		Obturators		Hypogastric		Ext. Iliacs		Com. Iliacs		Inguinals		Sacral	Aortics	Dist. metas.
	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT			
STAGE I (3)	–	–	–	–	–	–	1	1	–	–	–	–	–	–	–	1	–
STAGE II (10)	3	3	6	5	2	3	6	8	8	6	5	3	1	1	3	3	7
STAGE III (1)	–	–	–	–	1	1	–	1	1	1	1	–	–	–	1	–	–
STAGE IV (1)	1	1	–	1	1	1	–	–	–	1	–	1	–	–	–	1	1

B. *Carcinoma, Cervix Uteri,* fifteen treated cases (Table II).—

Clinical Stage I, three cases: The parametrium was fibrous but there was no evidence of metastasis. The channels were suggestively smaller than in the nontreated group and several of the nodes were completely hyalinized. One case had metastases to the hypogastric groups with one small cancerous node in the aortic group (two years postirradiation). All of these cases died of uremia secondary to ureteral obstruction (twenty-four, nine, and nineteen months, respectively, postirradiation).

Clinical Stage II, ten cases: Normal parametrium in two cases (twenty-nine and thirty-three months). Marked fibrosis of the parametrium occurred in five cases (thirteen, seven, nineteen, thirty-seven, and thirty-three months postirradiation). Nine of the cases had twenty-eight primary group nodes and nine secondary group nodes, and seven cases had distant metastases. Seventeen of the primary group nodes showed marked hyaline changes.

Clinical Stage III, one case: Two years following intensive irradiation, the parametrium was fibrous but free of metastasis. Nodes of both groups were involved and the patient died of uremia.

Clinical Stage IV, one case: Eighteen months after intensive irradiation, small isolated nodes with metastatic inclusions were present in the parametria; there were metastases to both node groups and the patient died from the metastases to the lung.

Node Involvement.[3, 4, 7, 26, 31, 33, 34, 38, 43, 44, 54]

Correlating the involvement of the lymph nodes in this relatively small series of treated and nontreated cases of carcinoma of the cervix, studied at necropsy, by careful dissection and multiple sections, several facts are apparent. This material is presented in Figs. 2 and 3.

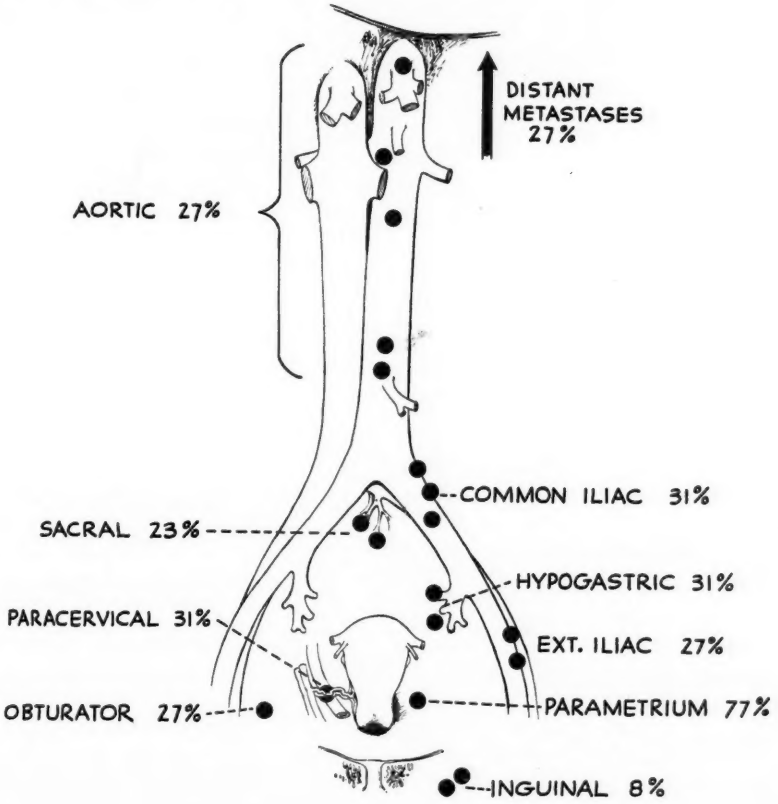

Fig. 2.—Incidence of node group involvement in twenty-six nontreated cases of cervical carcinoma.

Whereas the parametrium of the patients in the nontreated group revealed cancerous infiltration in 77 per cent of the cases, it occurred in only 33 per cent of the treated cases. The marked irradiation effect was manifested by extensive fibrosis of the parametrium, though in only approximately 70 per cent of the cases did the nodes show any of the changes usually attributable to deep irradiation. Nor were all of the small parametrial nodes containing metastases sterilized by the therapy. Whether the unaffected nodes were sterilized by the radiotherapy or were free of metastases before treatment cannot be stated. That the irradiation has some effect, is demonstrated by the lessened frequency of metas-

tases in the parametrium, and the increased frequency of distant metastases in the treated group. Therefore, on this small series, it is permissible to deduce that the irradiation probably destroyed some of the local metastases.

Distant metastases were present in 53 per cent of the treated and 27 per cent of the nontreated cases, suggesting the probable arresting effect of extensive irradiation on the local growth and involved nodes. That too much credence cannot be given this marked variation in incidence is supported by the presence of distant metastases in 37.8 per cent of the treated and 32.5 per cent of the nontreated cases in the entire series of 356 cases. This emphasizes the inherent danger of statistics based on a few cases. There was no involvement of the nodes of the secondary group without metastases present in the major primary nodes, though node involvement was present in two cases where there was no evidence of malignant extension to the parametrium.

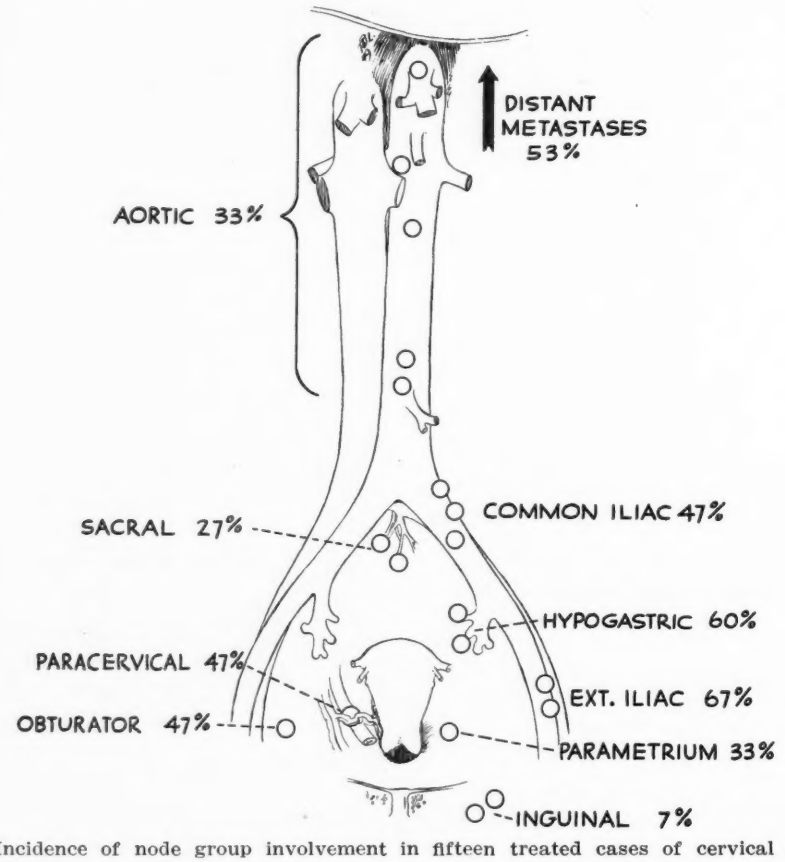

Fig. 3.—Incidence of node group involvement in fifteen treated cases of cervical carcinoma.

Part II

The 356 cases of cervical carcinoma, including the forty-one cases just described, are divided into a treated and nontreated group. Of the treated cases 42.6 per cent were treated under the auspices of the California Institute of Technology, the remainder either at the Los Angeles General Hospital or in private clinics. The material is set forth in Table III.

Node Involvement.—

The nontreated cervical series had a total of 44.7 per cent involvement of the primary group nodes, 39 per cent of the secondary group nodes, and 32.5

per cent with distant metastases. The treated series had an involvement of 58.5 per cent of the primary group nodes, 70 per cent of the secondary group nodes, and distant metastases in 37.8 per cent of the cases. Though the incidence of node group involvement varies considerably, the frequency of distant metastases is practically identical. Several factors must be considered in interpreting these differences; first, the variation in the time element as regards the clinical classification of the disease; second, the accepted 20 to 30 per cent error in the clinical interpretation of the stage of extension; third, the probable importance of radiotherapy as an impedimentary factor on the metastatic nodes.

TABLE III. INCIDENCE OF NODE GROUP INVOLVEMENT IN 356 NONTREATED AND TREATED CASES OF CERVICAL CARCINOMA

		PRIMARY NODES (PERCENT)	SECONDARY NODES (PERCENT)	DISTANT METASTASES (PERCENT)
Stage I	TREATED	85	85	41
	NON TREATED	2	–	–
Stage II	TREATED	77	65	37
	NON TREATED	20	4	2
Stage III	TREATED	50	58	26
	NON TREATED	31	27	15
Stage IV	TREATED	52	53	57
	NON TREATED	67	64	62
Total	TREATED	58.5	70	37.8
	NON TREATED	44.7	39	32.5

The involvement of 20 per cent of the primary group nodes in the nontreated *Clinical Stage II* cases is higher than expected. Of the 42.6 per cent treated at the California Institute of Technology, 50 per cent showed a local cure within a minimum of three months, a maximum of seven and one-half years, and an average of 2.8 years, following irradiation.

Distant Metastases.[1, 2, 5, 10, 19, 20, 37, 46, 52, 53, 54]

The frequency of distant metastases in cases of carcinoma of the cervix is not widely appreciated. This is especially true of those cases with pulmonary or bone metastases. Examining the material in Figs. 4 and 5 it is noted that distant metastases occurred in 32.5 per cent of the nontreated, and 37.8 per cent of the treated cases. The liver was the most frequent site of metastases, with the bone, lung, and bowel involved in that order. The slight variation in organ involvement in the two groups permits no significant explanation as to the effects of irradiation.

The unusual sites include the brain with occasional blindness. Several of the cases with bone metastases were treated as primary destructive bone lesions. There was primary involvement of the ureter in 2.1 per cent of the cases.[9, 13] The possible wide dissemination of the disease is further emphasized by the presence of metastases in the skin of the chest, the axillary nodes, the cervical nodes, the pituitary gland, and the parotid gland. The involvement of the left supraclavicular node (Virchow's node[49]) in the presence of cervical carcinoma is of interest since this node is usually mentioned as a common site of metastases from cancer of the stomach.

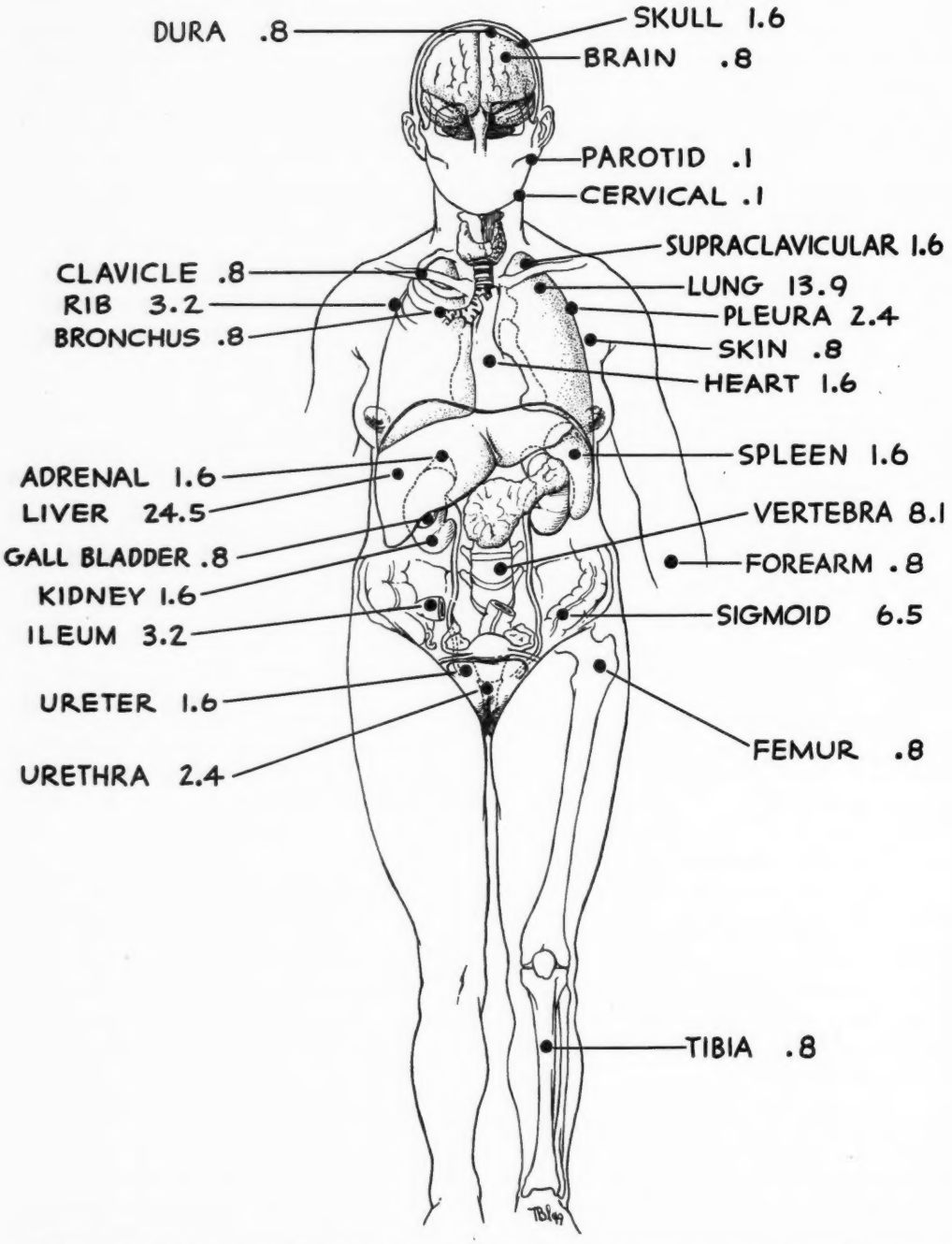

Fig. 4.—Incidence of distant metastases in 154 nontreated cases of cervical carcinoma.

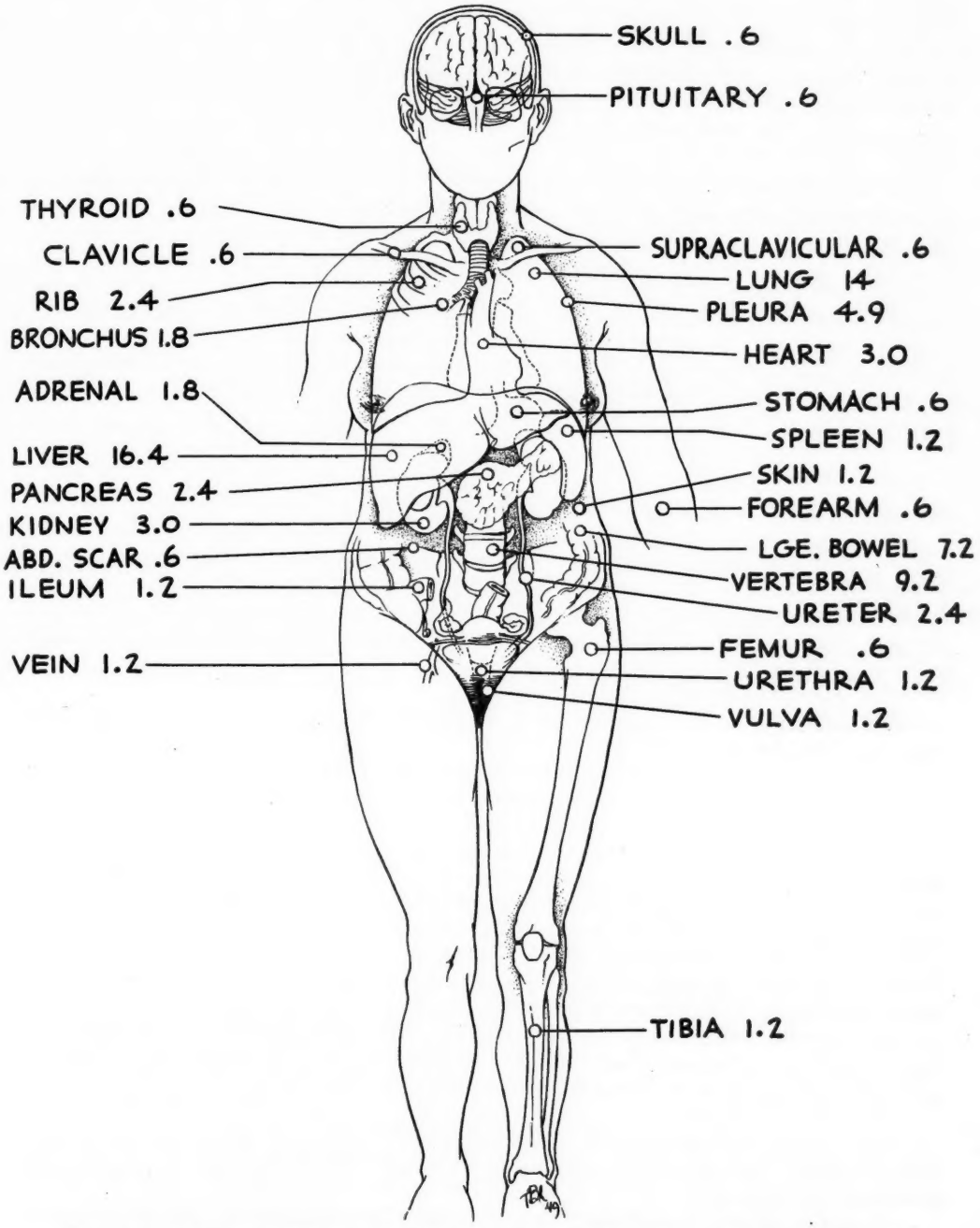

Fig. 5.—Incidence of distant metastases in 202 treated cases of cervical carcinoma.

The Assigned Cause of Death

In 1843, Dewees wrote that "patients rarely die during the carcinomatous stage of the disease; when they do, it is a consequence of frequent hemorrhage." Fifty years later, Dudley stated that, "in the vast majority of cases death is from marasmus or uremia, or both." Cullen in 1900 wrote that, "death is due to some intercurrent affection, usually to pneumonia or extensive renal disease." More recently, Warren and Ewing stated that complications arising from ureteral obstruction is the most common cause of death. This agrees with most observations.[5, 7, 10, 12, 18, 20, 26, 37, 50]

In this series, uremia was the assigned cause of death in 58.5 per cent of the nontreated cases and 49.3 per cent of the treated cases. However, an added 24.3 per cent of the nontreated cases had evidence of ureteral compression with hydronephrosis. In the treated series, the secondary ureteral involvement was 29.3 per cent, thus 82.8 per cent of the nontreated and 78.6 per cent of the treated cases had evidence of ureteral compression and kidney damage.[16, 17, 21, 25, 37, 42] Cachexia, hemorrhage, intestinal obstruction, and peritonitis accounted for the remainder of the patients dying as a result of this disease. There were 8.6 per cent of the nontreated and 6.4 per cent of the treated cases who died of causes unrelated to the malignant growth.

Part III

Adenocarcinoma, Corpus Uteri, sixty-four cases.—

The series of sixty-four cases of corporeal carcinoma does not permit the separation into treated and nontreated groups as none of the cases received irradiation therapy. The clinical stage of the extent of the cancerous growth follows the classification of Healey and Cutler,[24] and was established at the last admission of the patient to the hospital. In 14.2 per cent of the cases, the diagnosis was not made prior to autopsy.

The Lymphatic of the Uterus (Fig. 1).—

The rich plexus of lymphatics draining the corpus uteri converge to form three main channels.

Channel I: The lymphatic vessels from the lower and midportions of the uterus are closely associated with the major trunks from the cervix and metastasize in a similar pattern.

Channel II: The lymphatic vessels of the upper portion of the uterus join with the vessels from the adnexa and follow the direction of the ovarian vessels, draining directly into the nodes of the aortic group. Subsidiary vessels permit involvement of the primary and secondary node groups, as well as direct extension to the nodes at the level of the renal vessels.

Channel III: A lesser route, draining the fundus of the uterus, follows the course of the round ligament to the deep and superficial inguinal nodes.

Though there are three distinct channels, the rich anastomoses of lymphatic vessels permits no constant pattern of metastases based on the anatomical location of the cancerous growth within the uterus.

Node Involvement.—

The nodes and parametria of ten cases with corporeal carcinoma were carefully dissected and studied by multiple sections. The following material is also presented in Table IV.

Clinical Stage I, two cases: One case with a pyometra, probably secondary to radiotherapy eleven years previously for "cervicitis," was diagnosed at autopsy. The nodes of both groups, including the inguinal nodes, were markedly enlarged. Several of the nodes exhibited fibrosis and hyalinization, a change usually attributed to extensive irradiation. The second patient died from a cerebral accident, unrelated to the malignant growth.

Clinical Stage II, four cases: Microscopic metastases were present in the parametria of one case where the primary lesion was confined to the upper third of the uterus. This patient died of hemorrhage. In two cases, nodes of both groups were involved. One died of pneumonia following upper abdominal surgery; the second patient died of an acute nephritis. The fourth case had a direct metastasis to the aortic group and a small metastasis in the left adrenal gland. The lesion in this case was located on the right side of the fundus of the uterus.

TABLE IV. INCIDENCE OF NODE GROUP INVOLVEMENT IN TEN CASES OF CORPOREAL CARCINOMA

	Parametrium		Paracervical		Obturators		Hypogastric		Ext. Iliacs		Com. Iliacs		Inguinals		Sacral	Aortic	Dist. metas.
	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT	RT	LT			
STAGE I (2)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
STAGE II (4)	1	1	1	–	1	1	2	2	2	1	2	1	2	1	2	1	1
STAGE III (3)	1	1	–	–	1	–	–	–	–	–	1	1	1	–	–	2	2
STAGE IV (1)	1	1	–	–	–	–	1	1	1	1	1	1	1	1	1	1	1

Clinical Stage III, three cases: Parametrial involvement occurred in one case with metastases to the right obturator nodes (two nodes). The primary lesion was on the posterior wall just above the internal os. The patient died from severe cachexia and hemorrhage. In one case where the original growth was on the posterior wall of the uterus, metastases were found in the common iliac, the aortic, and the inguinal groups. The patient died of uremia; the exact cause was not determined. In the third case, with the lesion on the posterior and right walls of the uterus, the metastases went directly to the aortic group. Cases 2 and 3 had, in addition, distant metastases.

Clinical Stage IV, one case: The serosa of the uterus was perforated, but no contiguous involvement of the adjacent bowel or peritoneum was noted. With the exception of the paracervical and the obturator nodes, all groups of nodes were involved. The patient had distant metastases to the liver, mediastinal nodes, and the pleura. Death was due to a pyelonephritis.

The incidence of node and parametrial involvement in the ten carefully studied cases of adenocarcinoma of the corpus uteri is presented in Fig. 6. The higher frequency of metastases to the nodes of the secondary group emphasizes the tendency of this type of growth to follow the main lymph channels which drain directly into the aortic nodes. Intercommunicating vessels account for the metastases to the nodes of the common iliac group. Unilateral and cross metastases are not infrequent, and do occur, regardless of the anatomical location and clinical stage of the disease.

Despite the contrary impression, local and distant metastases are not infrequent in cases of adenocarcinoma of the body of the uterus.[23, 31, 32, 35] The following brief comments on the observations of sixty-four cases of corporeal adenocarcinoma, studied at necropsy, are also presented in Table V.

Clinical Stage I, eight cases: In one case where the lesion was on the anterior wall metastases occurred in the right hypogastric group. The parametrium was microscopically free of metastases and it is possible that this unusual site represents extension along an intercommunicating vessel from the ovarian trunk. Three of these cases had a pyometra with associated, benign enlargement of the nodes. The incidence of node disintegration is less severe than the changes present in nodes affected by intensive irradiation.

Clinical Stage II, eighteen cases: One case, with the lesion in the lower uterine segment, had involvement of the parametrium, the primary and secondary groups, and distant metastases to the liver. Two of the cases had metatases limited to the secondary group of nodes. Of the five cases with the metastases limited to the nodes of the aortic group, four had distant metastases. Eight cases had various degrees of pyometra associated with generalized nonmalignant enlargement of the nodes. Whether the associated pyometra increases the tendency to metastasize is questionable, but it is a definite possibility in view of the rapid and widespread extension of the inflammatory exudate to the lymph nodes.

Clinical Stage III, four cases: The parametrium and primary group nodes were involved in every case. The secondary groups were involved in three of the cases. Distant metastases were present in one case.

Clinical Stage IV, thirty-four cases: Carcinomatous involvement of the parametrium was present in twenty-four cases. The primary nodes were sites of metastases in fifteen cases, the secondary nodes in seventeen cases. In eight cases, the metastases were limited to the nodes of the aortic group. Seventeen of the thirty-four cases had diffuse peritoneal involvement and twenty-three cases had distant metastases.

TABLE V. INCIDENCE OF NODE GROUP INVOLVEMENT IN SIXTY-FOUR CASES OF CORPOREAL CARCINOMA

	PARA-METRIUM	PRIMARY GROUP	SECONDARY GROUP	INGUINAL NODES	AORTIC NODES ONLY	PERITO-NEUM	DISTANT METASTASES
Stage I (8)	—	1	—	—	—	—	—
Stage II (18)	1	1	3	3	5	—	4
Stage III (4)	4	4	3	1	—	—	1
Stage IV (34)	24	15	17	7	8	17	23

The histopathological changes in some of the lymph nodes were similar to those changes usually interpreted as indication of the effects of irradiation. The relative frequency of a pyometra in association with these hypertrophic nodes increases the difficulty of the gross interpretation of their exact histopathological status. The variation in size and palpable consistency of the nodes, in the presence of corporeal carcinoma, is greater than in similar nodes of the cases with cervical carcinoma. Unfortunately, we are unprepared to present the exact percentage of difference.

The route of lymphatic spread presents a fairly consistent pattern. All three channels can be followed in some instances, but for the majority of cases the rich intercommunicating vessels within the myometrium permit a frequent selection of either main channel despite the localized anatomical site of the cancerous growth. This series emphasizes the tendency of corporeal carcinoma metastases to involve directly the nodes of the aortic chain.

Including the seventeen cases with "frozen pelvis," 46 per cent of the series had malignant involvement of the parametrium; 33 per cent of the series had metastases to the nodes of the primary group and 36.5 per cent of the secondary group. The metastases were limited to the aortic group in 20.6 per cent of the cases. Distant metastases occurred in 44.4 per cent of the series.

Distant Metastases (Fig. 7)

Distant metastases, including the seventeen (26.9 per cent) cases with extensive carcinomatosis, were present in 44.4 per cent of the cases. The lungs, liver, ovary, bowel, pleura, adrenal gland, and the bones were the most frequent sites. The liver and the adrenal gland were the most common sites of metastases when the aortic group represented the only node involvement.

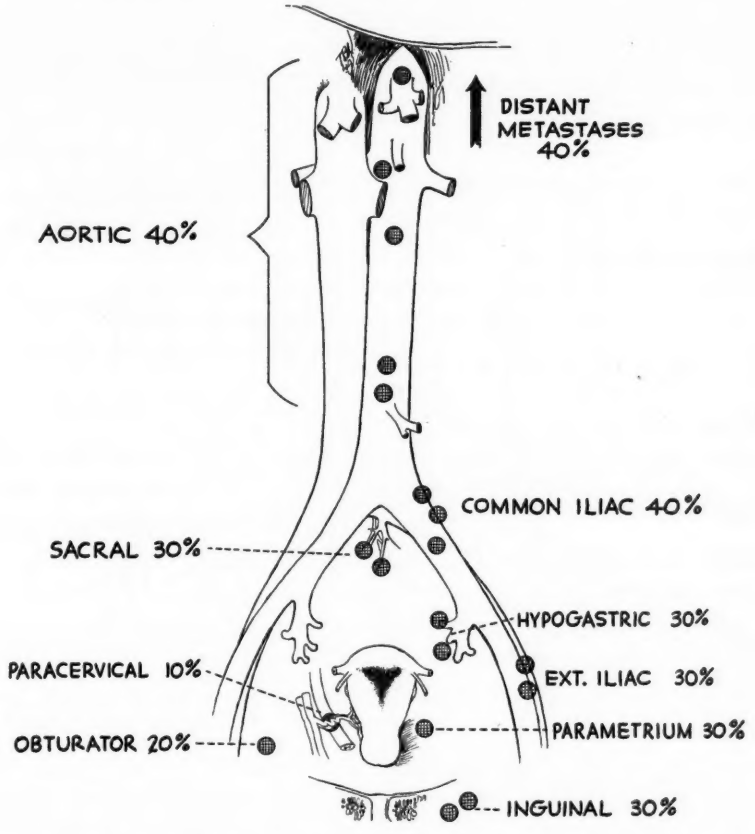

Fig. 6.—Incidence of node group involvement in ten cases of corporeal carcinoma.

The Assigned Cause of Death[31, 32]

Death due to causes unrelated to the malignancy occurred in 15.8 per cent of the cases. The assigned causes of death, attributable to the corporeal carcinoma, in order of frequency, were uremia and/or pyelonephritis (25.3 per cent), hemorrhage and/or cachexia (17.4 per cent), extensive carcinomatosis (15.8 per cent), pulmonary emboli or thrombosis (14.2 per cent), and peritonitis and/or intestinal obstruction (12.6 per cent). An additional 12.6 per cent of the series had various degrees of hydroureter and hydronephrosis and 28.6 per cent of the cases had pyometra; 14.2 per cent were not diagnosed correctly until autopsy.

Summary

1. The necropsy study of 420 cases of carcinoma of the cervix (356 cases) and the corpus uteri (64 cases) is presented with the incidence of lymph node involvement, distant metastases, and the assigned cause of death.

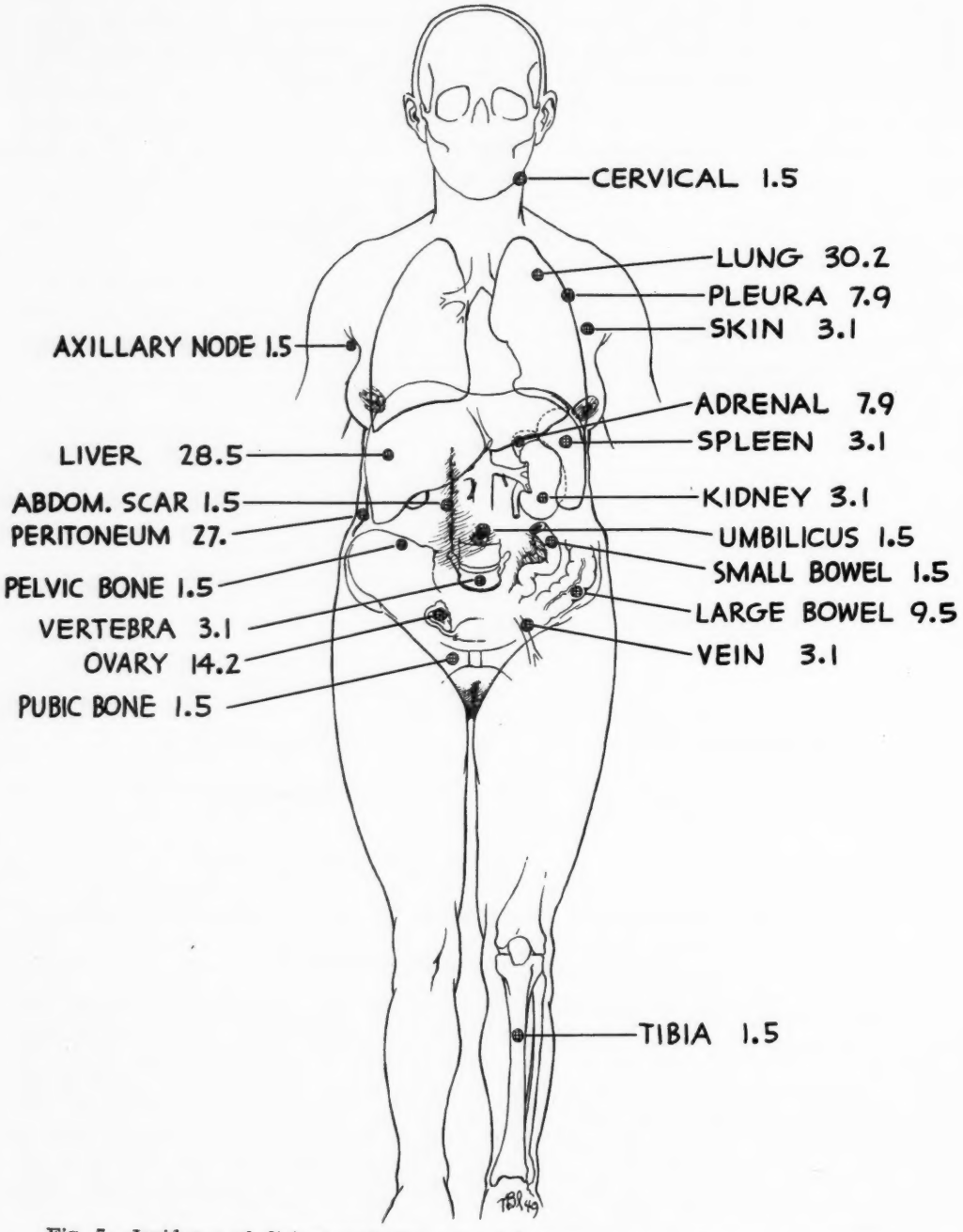

Fig. 7.—Incidence of distant metastases in sixty-four cases of corporeal carcinoma.

2. Careful dissection and multiple sections of the lymph nodes in twenty-six nontreated and fifteen treated cases of cervical carcinoma emphasize the frequency of early metastasis, the probable impedimentary effect of irradiation, and traces the routes of lymphatic spread. The parametrium was involved in 77 per cent of the nontreated cases and 33 per cent of the treated cases. Distant metastasis occurred in 27 per cent of the nontreated and 53 per cent of the treated cases.

3. In the series of 356 nontreated and treated cases of cervical carcinoma, the probable arresting effect of irradiation is emphasized by the difference in the node group involvement. The incidence of distant metastases varies little in the two groups.

4. The lymphatic spread, from cervical carcinoma, follows a constant course, the parametrium, the nodes of the primary group, and finally the secondary group nodes, before extension beyond the pelvis.

5. Uremia, the end result of ureteral compression, was the assigned cause of death in 58.5 per cent of the nontreated cases and 49.3 per cent of the treated cases. Evidence of ureteral obstruction and hydronephrosis was found in 82.8 per cent of the nontreated and 78.6 per cent of the treated cases.

6. The routes of lymphatic spread of endometrial carcinoma are less constant. The three main channels permit involvement of the same node groups as found in cervical carcinoma, or a by-passing of the primary groups with metastases directly to the inguinal nodes or the aortic nodes.

7. Uremia and/or pyelonephritis was the most frequent assigned cause of death in cases with endometrial carcinoma.

8. The disintegrating effects of irradiation does not occur in all of the treated cases, and similar changes, though usually of a lesser degree, are present in the nontreated cases. Histopathological changes are more frequent when there is a history of infection.

9. Histopathological evidence is lacking to support the claim that metastatic nodes may be sterilized by irradiation. The necropsy findings suggest the possibility of this effect.

10. The numerous intercommunicating lymphatic vessels account for the unpredictable sites of metastases.

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Discussion

DR. J. P. PRATT, Detroit, Mich.—The accumulation of such a wealth of material over a period of years shows a prodigious effort and faithful devotion to a worthy cause. As a result of his investigations, the author must have gained valuable impressions which would be difficult to put into words or communicate to others. The presentation of this interesting data suggests many questions relating to clinical investigation. It must have required considerable restraint not to digress.

By limitation of the subject to spread of carcinoma through the lymphatics other pathways have been excluded, namely, continuity, contiguity, and the blood vascular system. Distant metastasis (liver, lung, brain, bone) could hardly be explained by the lymphatic route alone. It seems likely that in many instances spreading occurred by more than one route and analysis of the cases so indicates. How would consideration of the other means of extension have altered the interpretation of lymphatic spread?

The reported error of approximately 20 per cent in the gross diagnosis of the lymph node status at necropsy is interesting. One could hardly expect to do as well at operation for the field of exploration is more limited. Yet it is necessary to act on one's judgment at the time, as it would be too long to wait for a pathologic report on each gland removed. This error in judging gross appearance of glands might well be used as an argument in favor of a radical operation in every case.

An error of more than 25 per cent in the clinical diagnosis of the extent of carcinoma is an important consideration. While the stages of invasion are well defined, it is often

difficult to place the lesion in the correct stage by clinical examination. Apparent cures of extensive lesions by radiotherapy may be open to question as to the diagnosis of the stage that was treated. Those who combine operation with radiotherapy will recall instances of an error in diagnosis as to the extent of the lesion.

The source of error varies, as is indicated in the following three examples: A patient with carcinoma of the cervix had an apparent extension into the left broad ligament. Radiotherapy appeared to shrink the cervical growth but the lesion in the broad ligament remained. When the uterus was removed at operation no vestige of malignancy remained in the cervix and the mass in the broad ligament proved to be endometriosis. A second patient had a carcinoma of the cervix and extensive induration in the broad ligament which preoperatively was thought to be malignant. After radiotherapy the induration in the pelvis improved. At operation the mass in the ligament proved to be due to a mixed infection. A third patient had clinical findings similar to the second patient. In this instance the induration of the broad ligament was part of a tuberculous peritonitis. In these instances the carcinoma of the cervix was in reality only Stage I or II at the most; they might well have been classed as Stage III or IV by clinical examination.

Carcinoma of the cervical stump as mentioned in thirty-two cases, i.e., more than 8 per cent, is a conspicuous occurrence. Do the records show whether the growth was present in the stump at the time the fundus was removed?

Extensive fibrosis of the parametrium was noted as an effect of irradiation. I have frequently been puzzled about the interpretation of induration in the pelvis at the time of follow-up examination. It has been assumed that symmetrical induration is probably an irradiation effect, while asymmetrical or nodular induration probably represents a recurrence of growth. Would the necropsy findings support this assumption?

Were there any distant metastases in treated patients who had no local recurrence in the pelvis? I had one patient with metastasis to the humerus discovered eight years after treatment. There were no recurrences in the pelvis.

Ureteral obstruction is an important item. Was it due to recurrence, invasion, or constriction by scar tissue? Parametrial involvement was reported in 77 per cent of the nontreated cases and only 33 per cent of the treated cases, but ureteral obstruction was nearly as common for the treated (78.6 per cent) as for the untreated (82.8 per cent). Should one infer that damage from irradiation is a cause of ureteral obstructions?

An important lesson to be learned from the material presented is the necessity of caution in comparison of statistics. Even at necropsy there was an error of 20 per cent in the interpretation of the gross appearance and 25 per cent in clinical diagnosis of the extent of the lesion. At best, statistical statements can only be relative.

DR. JOE V. MEIGS, Boston, Mass.—I feel very sure, at least I think I am right, that when a decision is finally made as to whether these patients should be operated upon or irradiated, according to their response to irradiation, that those who are irradiated but are radiation-resistant and do not respond well and die of the disease, will have very little involvement of the urinary tract. But in those who are sensitive and are given large doses and whom we hope to cure, we will cure the local disease but there will be involvement of the urinary tract. That is something we must find out about, irradiation sensitivity versus irradiation resistance. If Dr. Everett's analysis is accurate, we will find ureteral involvement due to irradiation in the sensitive patients and those patients who are free of this complication and are radiation-resistant will die of progression of the disease.

With reference to Dr. Henriksen's paper: In patients with carcinoma of the cervix we do a combination of the Wertheim operation and the Taussig operation; in other words, a radical hysterectomy with bilateral dissection of the pelvic lymph nodes. I am sure that in some cases I have not gone high enough and in some cases I am equally sure that I have not gone low enough. I think that is important.

This is true and important: in our usual operation for carcinoma of the endometrium we do a radical total hysterectomy but we do not routinely resect the lymph nodes. To my surprise, in one patient in whom I did a radical operation there were positive lymph nodes in the external iliac region. Dr. Henriksen's figures show you definitely where areas are

involved from carcinoma of the endometrium. Therefore, I think if we are to do surgery we must take the same attitude in carcinoma of the endometrium as we do in carcinoma of the cervix.

At this moment we are caught in a dilemma. Years ago we did a few radical operations for carcinoma of the cervix but we did not have suitable equipment and we had a desperate time. The treatment shifted to radium and x-ray and, recently, back to surgery. We lacked ability to recognize the importance of the surgical approach and there was a lack of knowledge of irradiation reactions. Eventually I think we will land in a position where we can say "this patient should be operated upon and this one deserves a decent amount of irradiation." Our problem is to select with good reason those cases which should be operated upon and those which should be irradiated, and this applies equally to carcinoma of the endometrium as it does to carcinoma of the cervix.

DR. CHARLES A. BEHNEY, Philadelphia, Pa.—Dr. Henriksen's careful study and excellent presentation are a great addition to our understanding of the spread of pelvic cancer. In a somewhat similar investigation of 166 patients who had died of cancer of the cervix, we regarded all extrapelvic lesions as metastatic because we could not distinguish between pelvic metastasis and extension by contiguity. We classified our cases of metastases as abdominal, thoracic, and skeletal, and these correspond to the author's "distant metastases." The distance from the primary tumor to the most remote point at which metastasis will be discovered is influenced by the cellular characteristics of the neoplasm and the time the patient survived after the onset of her disease. In our cases, metastases beyond the pelvis occurred in proportion to the anaplasticity of the tumor cells. Extension of carcinoma of the cervix via lymphatics is not unlike invasion of drain pipes by roots. If the incurable patient lives long enough, permeation will continue to distant regions.

DR. HENRIKSEN (Closing).—Both the clinical and pathological evidence points to the fact that metastases travel by the blood stream as well as by the lymphatics. However, to follow the vascular pathways would require years of study far beyond our facilities. We, therefore, confined this study to the routes of lymphatic spread and have listed the sites of the distant metastases without determining their itinerary. Invasion by direct extension is also a very important method of cancerous spread.

Of the thirty-two cases of carcinoma of the cervical stump, it is assumed that three of the cases were present at the time of surgery as they were found within six months following the subtotal hysterectomy.

The problem of the clinical interpretation of persistent or recurrent postirradiation parametrial induration remains unanswered. From observations at necropsy we do not subscribe to the tenet that asymmetrical or nodular induration is pathognomonic of residual or recurrent carcinoma. Another disturbing fact is that not infrequently a palpably normal parametrium contains lymph channels loaded with cancer.

Occasionally distant metastases are found in the treated cases with no demonstrable evidence of local activity. A careful study of the nodes of the primary and secondary groups will usually reveal nests of cancer cells within thickened lymph nodes. The gross findings in such cases are of little value.

Regarding the causes of ureteral obstruction in the treated cases, compression by either the residual or recurrent tumor growth is the most frequent finding; however, in this series, 2.2 per cent of the cases showed actual invasion and perforation of the ureteral wall. Irradiation may also affect the ureter causing an actual constriction or in the occasional case, a sloughing of the ureteral wall.

OVARIAN CARCINOMA*

A Review of 200 Primary and 51 Secondary Cases

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PROGRESS in improving the survival rate from cancer of the ovary in the past two or three decades has been relatively slight. The insidious onset of the disease frequently results in its early stages going unrecognized by the patient; it is also often unrecognized as such by the doctor. The site of the lesion renders it inaccessible to simple methods of anatomical diagnosis such as smears, biopsy, and curettage, as in the case of cervix and corpus uteri tumors. It is fortunately not a very common type of genital cancer, occurring next after cervix and fundus in frequency of carcinomas of the female genitals.[14]

I. Material and Method of Study

During the period 1922 through 1943 there were 200 cases of primary ovarian carcinoma of the ovary seen at the Sloane Hospital for Women. Both service and private patients are included in this number. There also were fifty-one cases of recurrent or metastatic (secondary) ovarian carcinoma seen during this period. This presentation is concerned only with the primary group and the secondary group will be but briefly mentioned.

The microscopic specimens of these 200 cases were all re-examined so that we should have a comprehensive approach to the study. This was done along with examination of all the benign papillary tumors that occurred during this same period. Some reclassification inevitably resulted, with the inclusion of one or two tumors not previously called malignant. At the same time the papillary carcinomas were graded according to degree of histological malignancy. This grading involves only the papillary serous group in so far as discussion of end results is concerned since the pseudomucinous group was too small to be statistically significant if broken down into subgroups.

Unless otherwise mentioned, all reference hereafter will be to the group of 200 primary cases.

II. End Results of 200 Cases of Primary Ovarian Cancer

A review of the literature reveals a marked inconsistency in the five-year survival rates of previous investigators. Table I presents a summary of the five-year cure rates of others in cancer of the ovary. The wide range of reported cure rates is most striking. The explanation for this variation undoubtedly lies in the criteria for making a pathological diagnosis of carcinoma of the ovary. Some investigators[8] feel that any papillary tumor of the ovary is malignant.

*Presented in condensed form at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

The decision to call a particular papillary serous cyst benign or borderline is often difficult to make and inconsistence in this respect undoubtedly further explains the great variation in end results presented from different parts of the country.[27-29] It is most unlikely that surgical and radiation techniques in various parts of the country are so much different that they would produce this wide range of results.

TABLE I. STATISTICS OF VARIOUS AUTHORS, FIVE-YEAR CURE RATES IN CANCER OF THE OVARY

AUTHOR	YEAR	NUMBER OF CASES	FIVE-YEAR CURE RATE (PER CENT)
Straussman	1921	17†	8.5
Schafer	1922	70*	13.0
Ford	1928	59†	28.8
May	1930	†	31.0
von Peham and Amreich	1930	115*	9.5
Heyman	1932	134†	31.3
Anspach	1934	24	29.1
Norris	1934	44	50.0
Harris and Payne	1935	51*	51.0
Murphy	1935	92†	24.0
Lynch	1936	64	35.5
Jacobs and Stenstrom	1937	31	35.4
Counseller	1940	143*	65.4
		118†	50.5
		36‡	16.7
Meigs	1940	154	15.5
Pemberton	1940	114	32.0
Jones	1941	30	23.3
Walter, Bachman, and Harris	1941	63*	6.3
		61†	22.9
Taylor and Greeley	1942	138	15.2
Helsel	1946	100	20.0
Campbell and Singman	1947	69	13.0
Swinton and Yancey	1947	45	14.0
Munnell and Taylor	1949	200	27.5

*Surgery alone.
†Surgery and x-ray.
‡X-ray alone.

TABLE II. THE FIVE-YEAR END RESULTS OF 200 PRIMARY CASES OF CARCINOMA OF THE OVARY (Sloane Hospital for Women, 1922 Through 1943)

	A	B		C	D		
		INDETERMINATE				RELATIVE FIVE-YEAR CURE RATE D/C (PER CENT)	ABSOLUTE FIVE-YEAR CURE RATE D/A (PER CENT)
HISTOLOGIC TYPE	TOTAL CASES	WELL WHEN LOST	DIED OF OTHER CAUSES	DETERMINATE REMAINDER A-B	TOTAL FIVE-YEAR CURES		
Papillary serous cystadenocarcinoma	125	18	1	106	38	35.8	30.4
Undifferentiated papillary adenocarcinoma	22	-	-	22	0	0	0
Papillary pseudomucinous cystadenocarcinoma	15	1	-	14	9	64.2	60.0
Granulosa cell tumor	13	2	-	11	7	63.6	53.8
Dysgerminoma	3	-	-	3	1	33.3	33.3
Unclassifiable	10	-	-	10	0	0	0
Clinical diagnosis (no operation)	12	-	-	12	0	0	0
Over-all Totals	200	21	1	178	55	30.8	27.5

The five-year end results of the 200 cases of primary carcinoma of the ovary seen at Sloane Hospital for Women in the period 1922 through 1943 are presented in Table II. Two different survival or cure rates are given, the relative and the absolute. The absolute survival rate is based upon the total number of patients seen. The relative survival rate is derived from the "determinate" cases, that is, by excluding patients who died of other disease or who were lost to follow-up but well at the time they were lost. In this determinate group those who had residual or recurrent disease at the time they were lost are considered dead of cancer.

The over-all relative five-year survival rate for the 200 cases was 30.8 per cent and the absolute rate was 27.5 per cent. Papillary pseudomucinous cystadenocarcinoma and granulosa cell tumors were the two most favorable types with relative cure rates for each being above 60 per cent. No five-year survivals resulted in those patients with undifferentiated adenocarcinoma, unclassifiable carcinoma or those who were not operated upon. Almost two-thirds of the total group were patients with papillary serous cystadenocarcinoma; the five-year survival rates for this group are close to the over-all figures, being 35.8 per cent relative and 30.4 per cent absolute.

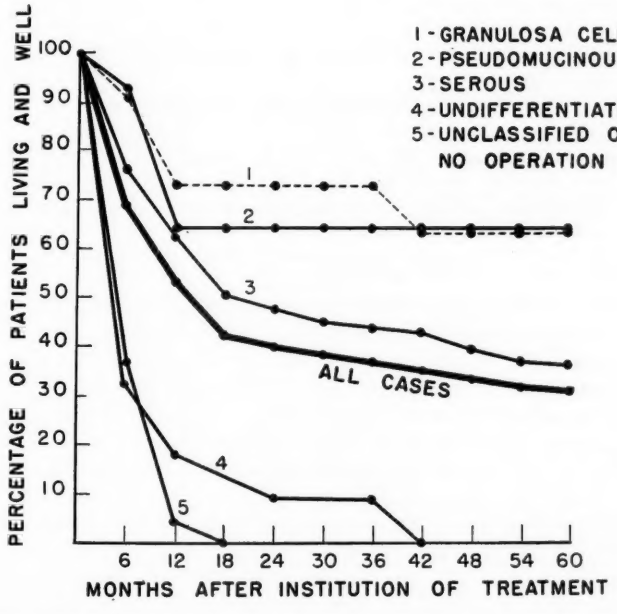

Fig. 1.—Five-year survival curves in carcinoma of the ovary according to histological type.

Points on a five-year survival curve of the determinate cases were calculated for each six months following treatment and the results are shown in Fig. 1.* It will be noted that at the end of one and a half years almost 60 per cent of the patients had died and that thereafter the curve drops much more slowly so that at the end of five years' time it has dropped only another 10 or 12 per cent. This extensive loss of life within the first year and a half after treatment is begun testifies to the malignancy of this type of genital cancer.

*Attention should be called to the theoretical and practical advantage of survival curves of the type shown in Fig. 1. Such curves can be used as a baseline for the evaluation of a new type of treatment over the old in different types of cancer before five years have elapsed. Obviously, the number of cases involved must be of statistical significance.

III. End Results of Fifty-One Cases of Secondary Ovarian Cancer

The five-year end results of fifty-one cases of recurrent or metastatic ovarian carcinoma are presented in Table III. There were no five-year survivors of the three patients with recurrent ovarian cancer or of the eighteen cases of ovarian carcinoma metastatic from the stomach or colon. The twenty-eight cases of carcinoma of the ovary metastatic from the fundus uteri include those with both gross or microscopic metastases; nine of these lived five or more years after treatment was instituted. There was only one case of adenocarcinoma metastatic from the breast and one case of a melanosarcoma metastatic from the eye; neither survived.

TABLE III. FIVE-YEAR END RESULTS. RECURRENT AND SECONDARY OVARIAN CARCINOMA

PRIMARY SITE	TOTAL CASES	RELATIVE FIVE-YEAR CURE RATE	ABSOLUTE FIVE-YEAR CURE RATE
Recurrent	3	0	0
Stomach and colon	18	0	0
Fundus	28	(9) 37.5%	32.1%
Eye	1	0	0
Breast	1	0	0

No further reference to this secondary group will be made.

IV. Factors Determining Prognosis

A. Histogenetic Type of Tumor.—

The importance of the histological type of tumor encountered in determining prognosis is evident from examining comparative cure rates in Table II and Fig. 1.

B. Histological Degree of Malignancy.—

The importance of the histological degree of malignancy in relation to the five-year survival rate is most apparent in the 125 cases of papillary serous cystadenocarcinoma which made up the bulk of the series. In the course of reexamining and classifying the histological specimens of the 200 primary cases they were graded according to histological degree of malignancy. The papillary serous carcinomas were divided into four grades: borderline, Grade I, Grade II and Grade III, in order of progressively greater degrees of malignancy.

TABLE IV. THE END RESULTS OF 125 CASES OF PAPILLARY SEROUS CYSTADENOCARCINOMA ACCORDING TO HISTOLOGICAL GRADE OF MALIGNANCY
(Sloane Hospital for Women, 1922 through 1943)

	A	B INDETERMINATE		C	D		
HISTOLOGICAL GRADE OF MALIGNANCY	TOTAL CASES	WELL WHEN LOST	DIED OF OTHER CAUSES	DETERMINATE REMAINDER A-B	TOTAL FIVE-YEAR CURES	RELATIVE FIVE-YEAR CURE RATE D/C (PER CENT)	ABSOLUTE FIVE-YEAR CURE RATE D/A (PER CENT)
Borderline	28	8	1	19	17	89.8	60.7
Grade I	29	6	0	23	14	60.8	48.2
Grade II	19	1	0	18	4	22.2	21.0
Grade III	49	3	0	46	3	6.5	6.1
Group Total	125	18	1	106	38	35.8	30.4

Table IV presents the five-year survival rates for this group of papillary serous cystadenocarcinomas and very clearly shows the direct relationship between

histological degree of malignancy and end results. The borderline group provided the highest percentage of five-year survivors, 89.8 per cent relative and 60.7 per cent absolute. There was a progressive and rapid decrease in the next three groups, 48.2 per cent for Grade I, 21.0 per cent for Grade II, and 6.1 per cent for Grade III. Fig. 2 presents the five-year survival curves for this group.

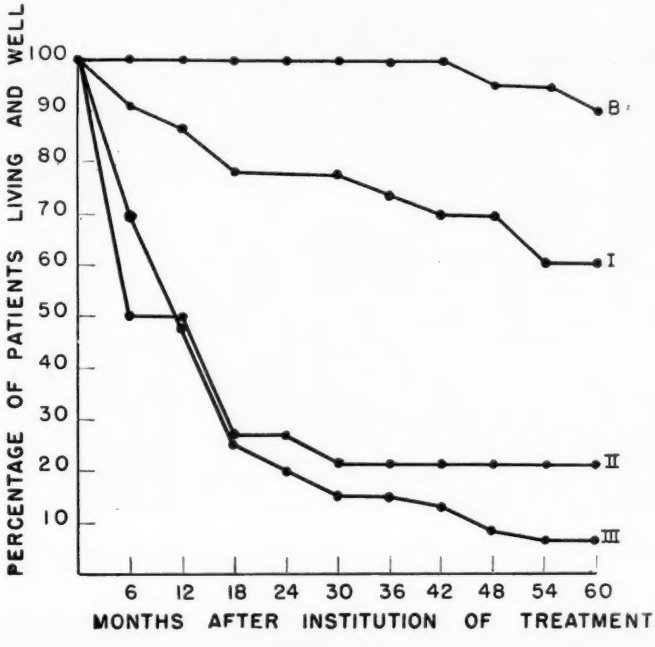

Fig. 2.—Five-year survival curves for papillary serous cystadenocarcinoma according to degree of histological malignancy.

Although the use of the term "borderline" suggests that there is some question as to whether or not the tumor is properly called cancer, it is our belief that this group is truly malignant. The "borderline" papillary serous cystadenocarcinoma has long presented the pathologist with difficulty in making this decision. By virtue of the fact that there were included in this group of twenty-eight "borderline" cases those of a fairly uniform histological appearance, and since there were two five-year failures among the nineteen traced cases, it follows that the remaining seventeen successfully treated cases represented true carcinomas. Further support to this impression is gained from the fact that there were three failures *after* five years in this group; further mention will be made of these three cases later. Briefly, the criteria for placing a papillary serous tumor in this borderline group include: (1) some degree of cellular anaplasia, (2) excessive papillary formation, (3) invasion of the stroma by adenomatous elements, and (4) some piling up of the epithelium. Figs. 3 and 4 are photomicrographs of a case of borderline papillary serous cystadenocarcinoma showing some of these characteristics.

C. Clinical Extent of Disease.—

The 200 primary cases were divided into four clinical stages according to extent of cancer as determined at operation. Clinical Stage I includes those cases with involvement of one ovary alone; Stage II includes those with both ovaries involved; Stage III includes those with one or both ovaries involved together with spread to pelvic peritoneum or viscera (Fallopian tubes excluded);

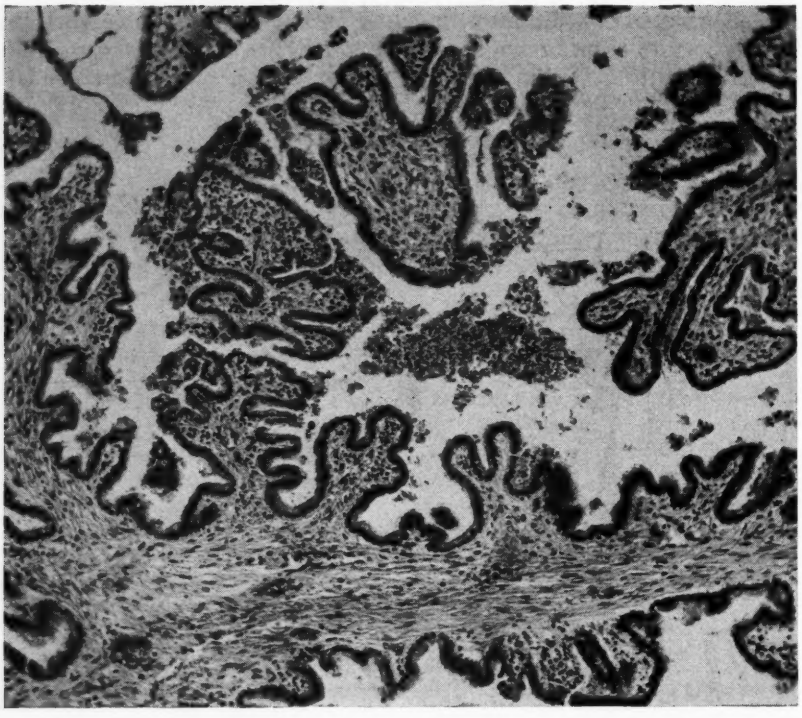

Fig. 3.—Bilateral ovarian cysts treated by bilateral salpingo-oophorectomy. Original pathological diagnosis was papillary serous cystadenomas. This picture is of the original tumor.

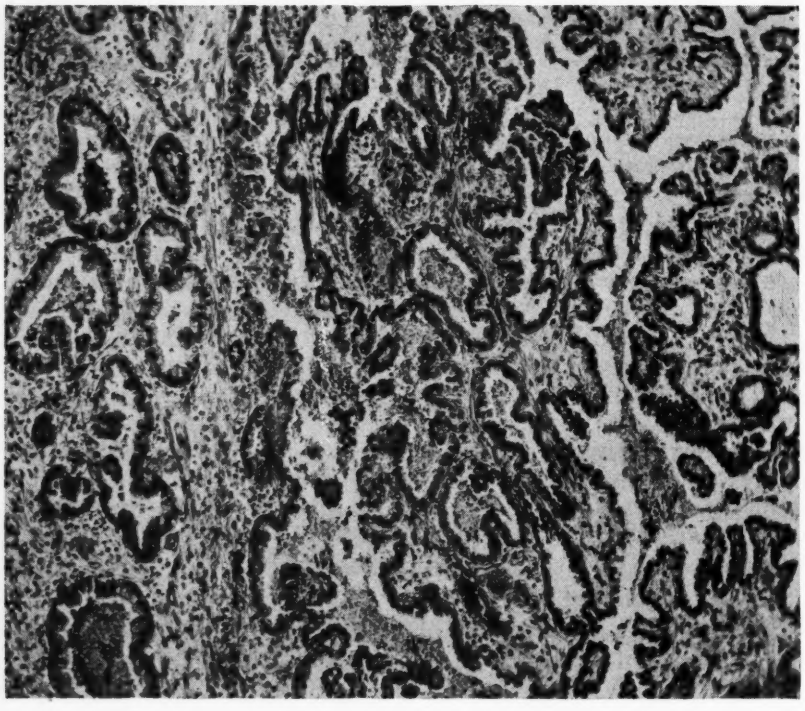

Fig. 4.—Same patient as shown in Fig. 3. Showing the recurrence twelve years later. Now called a low-grade papillary serous cystadenocarcinoma.

Stage IV includes those with involvement of ovaries and pelvis with spread to the upper abdominal peritoneum or viscera. As shown in Tables V and VI the best five-year survival rates are obtained when there has been no spread beyond the ovaries. Whether ovarian involvement is unilateral or bilateral does not seem important in prognosis. As a matter of fact, the Stage II results are superior to the Stage I results but this is probably a statistical accident. What is important is the matter of localization of tumor to the ovaries. As soon as spread outside the ovaries occurs, the chances for five-year survival drop precipitously.

TABLE V. END RESULTS OF OVARIAN CARCINOMA RELATED TO EXTENT OF DISEASE
(Based on Determinate Cases Only)
(Sloane Hospital 1922-1943)

CLINICAL STAGES	TOTAL CASES	FIVE-YEAR CURES	
		NUMBER	PER CENT
Stage I One ovary only involved	51	30	59
Stage II Both ovaries involved	20	16	80
Stage III Extension to pelvic peritoneum and/or pelvic viscera	25	5	20
Stage IV Extension to abdominal peritoneum and/or viscera	82	4	5
Totals	178	55	27.5

TABLE VI. FIVE-YEAR CURE RATE IN OVARIAN CARCINOMA RELATED TO EXTENT OF DISEASE
(DETERMINATE GROUP ONLY)

HISTOLOGICAL TYPE	I			II			III			IV		
	TOTAL CASES	FIVE-YEAR CURES		TOTAL CASES	FIVE-YEAR CURES		TOTAL CASES	FIVE-YEAR CURES		TOTAL CASES	FIVE-YEAR CURES	
		NUMBER	PER CENT		NUMBER	PER CENT		NUMBER	PER CENT		NUMBER	PER CENT
Papillary serous cystadenocarcinoma												
Borderline	4	4	100	9	9	100	4	3	75	2	1	50
Grade I	6	5	83	8	7	87	5	1	20	4	1	25
Grade II	5	4	90	2	0	0	2	0	0	9	0	0
Grade III	13	2	15	1	0	0	6	1	16	26	0	0
Undifferentiated papillary adenocarcinoma	3	0	0	0	0	0	3	0	0	16	0	0
Papillary pseudomucinous cystadenocarcinoma	9	7	78	0	–	–	2	0	0	3	2	67
Granulosa cell tumor	9	7	78	0	–	–	1	0	0	1	0	0
Dysgerminoma	1	1	100	0	–	–	0	–	–	2	0	0
Unclassifiable	1	0	0	0	–	–	2	0	0	7	0	0
Clinical diagnosis	0	–	–	0	–	–	0	–	–	12	0	0
Totals	51	30	58.8	20	16	80	25	5	20	82	4	4.8

Of the nine survivors of five years or more in clinical Stages III and IV all but one were of low-grade histological malignancy. Four were borderline serous carcinomas, two were Grade I serous carcinomas, two were pseudomucinous carcinomas and only one was a Grade III serous carcinoma (Table VI).

Clinical extent of disease is considerably dependent upon the histological type and degree of histological malignancy. The tumors of high-grade malignancy are more frequently found to have spread outside the ovaries by the time the patient comes to operation.

V. Management

Some type of surgery was carried out in 188 of the 200 cases. This ranged from exploratory laparotomy to complete removal of the internal genitalia. Surgery remains the fundamental part of the treatment of carcinoma of the ovary.

A. Surgical Management of the Unilateral Ovarian Carcinoma.—

Of considerable interest, albeit confusing, is Table VII showing the five-year survival rates in patients with *unilateral* ovarian carcinoma. Of forty-six patients with only one ovary malignant, one-half had radical surgery performed (bilateral salpingo-oophorectomy and hysterectomy) and one-half had conservative surgery performed (conservation of the uninvolved ovary with or without conservation of the uterus). The five-year survival rates for the two groups are essentially the same, a fact mentioned by previous investigators.[17] None of these conservatively treated patients was reoperated upon and only nine of them received postoperative x-ray therapy. Two patients, both with unilateral pseudomucinous carcinomas, subsequently had normal pregnancies.

TABLE VII. RELATION OF TYPE OF SURGERY TO FIVE-YEAR CURE RATE IN CLINICAL GROUP I CASES
(One Ovary Alone Involved)

	CONSERVATIVE SURGERY			RADICAL SURGERY		
	TOTAL NUMBER	FIVE-YEAR CURES		TOTAL NUMBER	FIVE-YEAR CURES	
HISTOLOGICAL TYPE	TREATED	NUMBER	PER CENT	TREATED	NUMBER	PER CENT
Papillary serous carcinoma						
Borderline	2	2	100	2	2	100
Grade I	4	3	75	2	2	100
Grade II	2	1	50	3	3	100
Grade III	6	1	17	7	1	14
Pseudomucinous carcinoma	3	3	100	6	4	67
Granulosa cell	6	4	67	3	3	100
Totals	23	14	61	23	15	65

In spite of these results which seem to indicate that unilateral oophorectomy is adequate treatment for a unilateral ovarian carcinoma that has spread no further, we cannot subscribe to a policy of conservatism in treating such cases. To the contrary, it appears probable that some of the failures in the unilateral oophorectomy group were due to preservation of the apparently sound ovary and had bilateral oophorectomy been the rule for the one-sided tumors, the results in Stage I cases might have been as good as for Stage II. Further, there were a few cases included in this series of 200 patients in whom radical surgery was carried out for what was thought to be a unilateral tumor but in whom histological examination of the apparently normal ovary revealed microscopic carcinoma. Had these few cases of gross carcinoma in one ovary and

microscopic carcinoma in the other ovary been treated conservatively, they would undoubtedly have significantly lowered the survival rate of the conservatively treated group.

We agree with the principles of Meigs[16] and others, that radical surgery be performed if the tumor is papillary except in rare instances where perhaps the patient is young and childless. Here, if the gross appearance of the tumor suggests one of low-grade malignancy and if the opposite ovary seems perfectly normal, the latter and the uterus may be retained.

We cannot confirm or refute Meigs' belief in the *necessity* for total rather than subtotal hysterectomy since most hysterectomies in this series were subtotal. However, as a general rule, total hysterectomy should always be the preferred routine procedure if for no other reason than to prevent the subsequent development of carcinoma of the cervical stump.

B. Postoperative X-ray Therapy.—

The value of postoperative radiation has been the subject of considerable discussion in the literature on ovarian carcinoma with wide divergence of opinion as to its value. The radiation therapists champion its use both as a palliative and curative agent.[2, 5, 7, 10, 12, 15, 16, 19, 25] Most gynecologists have no real conviction as to its therapeutic value[3, 11, 14] while a few have considered it to be not only of no value but actually injurious.[6, 20]

Five-year survival curves of the determinate cases treated with surgery alone and surgery plus x-ray according to histological type and degree of malignancy and according to extent of disease are shown in Figs. 5 and 6. The two factors, histological type and degree of malignancy and clinical extent of disease, should be considered jointly in attempting to determine the value of irradiation therapy as an adjunct to surgery in different situations.

In cases of tumors of low-grade malignancy such as borderline and Grade I papillary serous cystadenocarcinomas the survival curves for surgery alone are better than those for surgery plus x-ray. However, this does not mean that x-ray therapy was the cause of the poorer results in the surgery plus x-ray group; the actual reason for the poorer result in surgery plus x-ray treatment of the borderline and Grade I serous cases was that the failures, with one exception, were patients with such extensive spread of disease that they were in clinical Stages III and IV. The same explanation holds for the poorer results from surgery and x-ray in the papillary pseudomucinous cystadenocarcinoma group.

On the other hand, the survival curves for the surgery plus x-ray cases in the more malignant histological type of tumors, the Grades II and III serous carcinomas, and the undifferentiated and unclassifiable carcinomas, are better than the survival curves for surgery alone. This is probably a true picture although not a very bright one considering how very low the five-year survival results for these tumors are. Nevertheless, the only five-year survivors in the Grade III serous cases were those who received postoperative radiation. In the undifferentiated adenocarcinomas, although not curative, radiation therapy certainly seemed to prolong life, providing a moderate palliative effect.

In the survival curves based on clinical extent of disease, the superior results from surgery alone in the clinical Stages I and II do not indicate that supplementary x-ray is harmful but they do make its value very questionable. In the more widespread clinical stages of disease, Stages III and IV, postoperative x-ray therapy increased life survival time.

It would appear from this series that postoperative x-ray therapy is of value in some instances and not in others. Its value seems definite in all cases of extensive spread, clinical Stages III and IV, at least from a palliative, and occasionally from a curative, point of view. It is of no value in tumors of low-

grade malignancy limited to the ovaries. In localized tumors of higher degrees of malignancy its value is questionable except perhaps from the palliative point of view.

Certainly radiation therapy should not be withheld from the apparently hopeless case for in two cases in this series it converted inoperable cases into operable ones. Both patients had papillary serous cystadenocarcinoma, were explored and found to be inoperable, given x-ray therapy and operated upon again (one a year later, the other two years later) when clinical examination indicated a favorable change had occurred. One patient is living and well after fifteen years; the other died after four years, possibly of another disease.

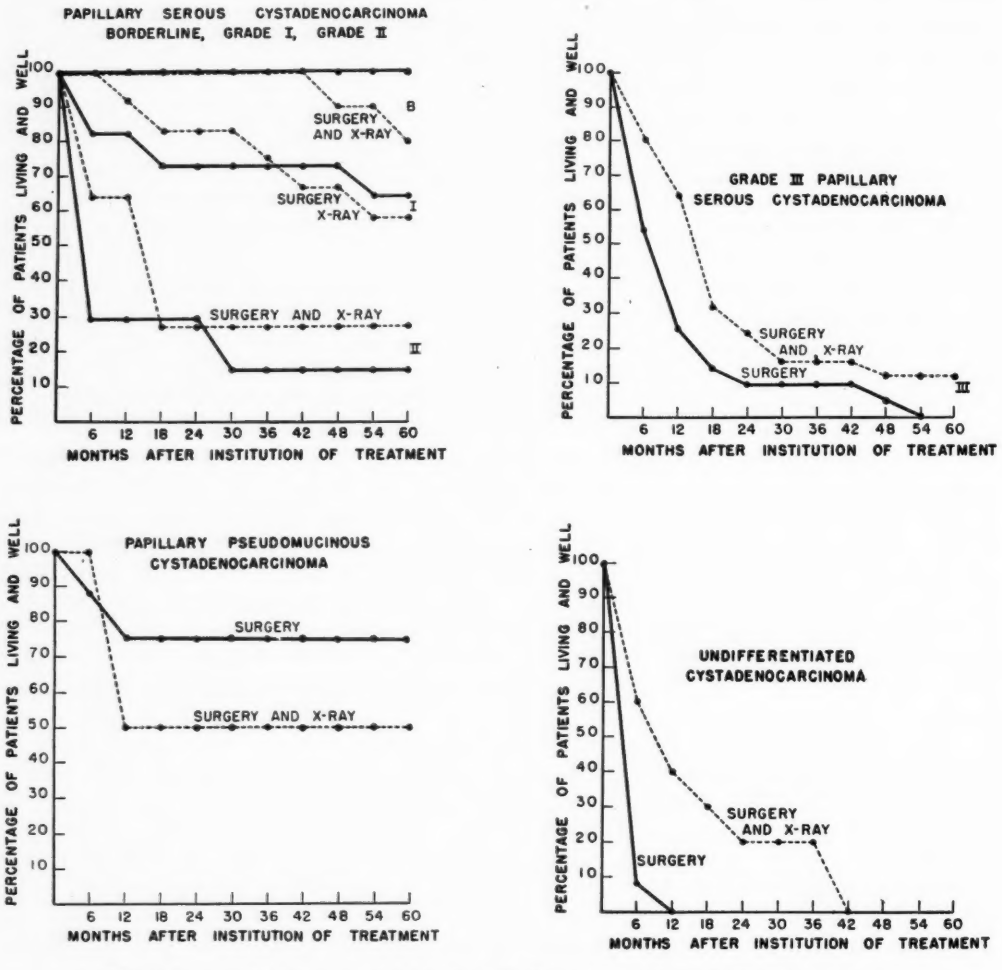

Fig. 5.—Survival curves—histological malignancy and method of treatment.

VI. Granulosa Cell Tumors

There were thirteen granulosa cell tumors seen during this period and included in this series. Their inclusion increases the five-year survival rate by about 5 per cent since it is a tumor generally of low-grade malignancy. Only two patients received postoperative x-ray therapy and both died. There were only seven successfully treated cases in this group. This is a recurrence rate of 36 per cent, as compared with that of 28.0 per cent of Novak and Brawner.[23]

TABLE VIII. RECURRENCE AND/OR DEATH AFTER FIVE YEARS

HISTOLOGICAL TYPE	YEAR									TOTAL DEATHS AFTER FIVE YEARS
	6	7	8	9	10	11	12	13	14	
Papillary serous cystadenocarcinoma										
Borderline	1		1						1	3
Grade I				1		1	1			3
Grade III		1								1
Pseudomucinous cystadenocarcinoma	1									1
										8

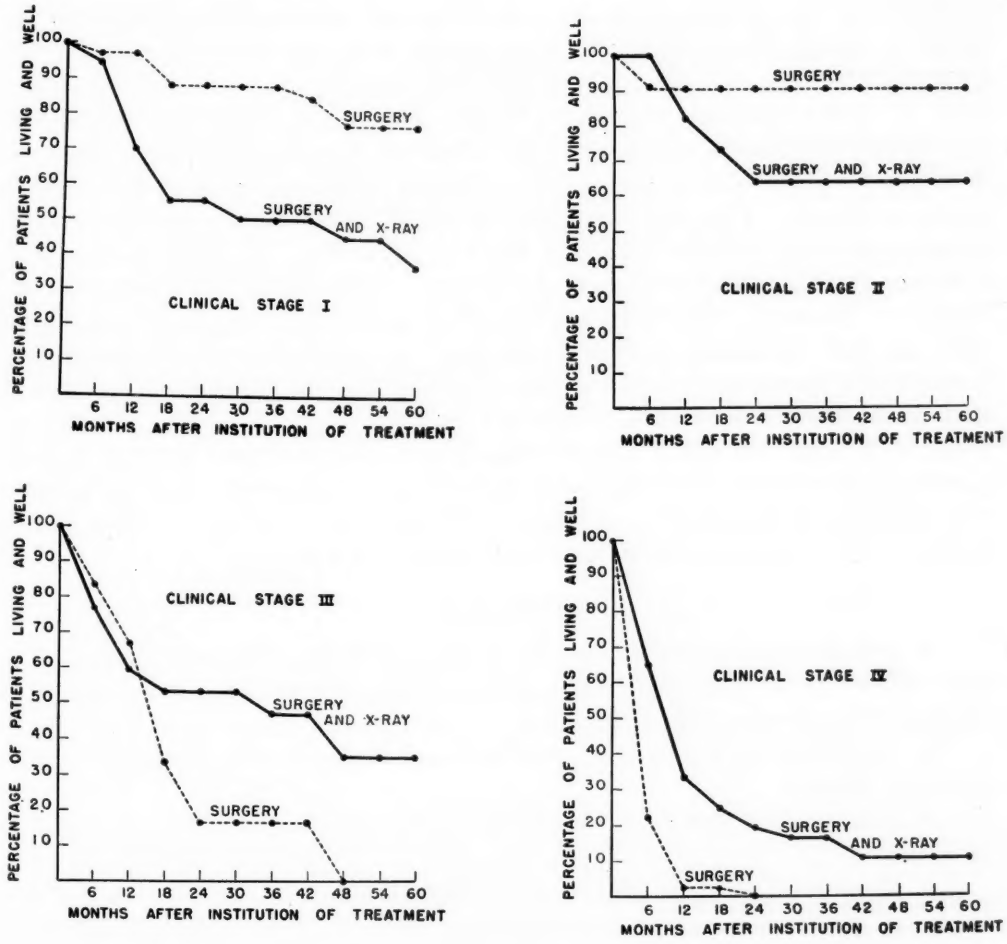

Fig. 6.—Survival curves—clinical extent of disease and method of treatment.

VII. Recurrence and Death After Five Years

Five-year survival in postoperative ovarian cancer does not mean permanent cure. There were eight patients with recurrence or death after five years. Six of the eight were patients with papillary serous cystadenocarcinomas of border-

line or Grade I malignancy. One-half of these had originally had conservative surgery for localized cancer; later recurrence in these three cases is further evidence in support of the principle of radical surgery. Three others had extensive disease, but of low-grade malignancy and received postoperative x-ray so that they lived for many years in spite of not having had complete removal of the tumor. Time of recurrence or death is shown in Table VIII.

Discussion

Carcinoma of the ovary is still one of the least curable cancers of the female genitals. In this series 64 per cent of the patients had gross evidence of peritoneal or visceral metastases at the time of operation; in the absence of gross metastases microscopic transperitoneal or lymphatic metastases may have already occurred. Early diagnosis has been stressed as the most important means available at the present time for improving the survival rate. Lynch[13] has shown a correlation of duration of symptoms with survival. The present-day program of cancer education emanating from both lay and professional sources with an ever-increasing number of women presenting themselves periodically for routine examination should certainly increase the number of early diagnoses. Whether or not this is going to effect ovarian cancer survival appreciably remains to be seen. Twombly[30] reports that out of forty patients in whom ovarian cancer was discovered prior to the onset of symptoms (i.e., found on routine examination for other causes or developing while under observation at the Memorial Hospital), *none* survived five years and 50 per cent were dead within nine months. Certainly an inescapable fatalistic conclusion comes from our own series which shows so clearly the importance of the histological type of tumor and the histological degree of malignancy in determining prognosis. The future must offer more than early clinical diagnosis if ovarian cancer survival is to be materially increased. Perhaps this will be a method affording early histological or cytological diagnosis that will precede clinical signs; perhaps it will be higher voltage x-ray or improved methods of administering radiation.

Summary

1. Two hundred cases of primary carcinoma of the ovary with at least five-year follow-up are presented. The papillary serous cystadenocarcinomas make up almost two-thirds of the total series.

2. The five-year over-all survival rates are 30.8 per cent absolute and 27.5 per cent relative.

3. The so-called borderline papillary serous cystadenocarcinoma is a malignant tumor.

4. Prognosis depends chiefly upon the histogenetic type of tumor and upon the histological degree of malignancy, both of which largely control the clinical extent of disease. Ovarian tumors of low-grade histological malignancy have the most favorable prognosis. Similarly, tumors still confined to the adnexa are most favorable to treat. Clinical extent of disease is usually greater in tumors of high-grade histological malignancy.

5. The following tumors are regarded as being of low-grade histological malignancy; papillary serous cystadenocarcinoma, borderline and Grade I;

most papillary pseudomucinous cystadenocarcinomas; and most granulosa cell tumors. The best chances for survival occur in these cases.

6. Complete surgical removal of the internal genitals remains the treatment of choice in ovarian carcinoma. Conservative surgery is rarely justifiable.

7. Radiation therapy has a definite place in the treatment of certain cases of ovarian carcinoma chiefly to prolong survival time and perhaps occasionally (although rarely) to cure residual disease. It should be administered to all patients with tumors of high-grade histological malignancy even if localized to one or both ovaries. It seems of no value in tumors of low-grade histological malignancy unless there is operative evidence of spread beyond the ovaries; in the latter event, x-ray should be given. It should be given to all patients with extension of tumor beyond the ovaries regardless of the amount of spread and regardless of histological type.

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Discussion

DR. WILLIAM MENGERT, Dallas, Texas.—Carcinoma of the ovary numerically ranks third among female genital carcinomas. Those of us with ward services see it infrequently and the average gynecological surgeon does not often encounter it. Consequently, Dr. Taylor and his associate, Dr. Munnell, are to be congratulated for presenting the results of such a large series. The work was thorough and the conclusions from the facts presented seem eminently sound.

Carcinoma of the ovary is a "silent" lesion, since the tumor has reached a considerable stage of development by the time it manifests itself to the patient. Moreover, there is an appreciable group arising in previously existing cystadenomas, although many primary ovarian cancers develop as such. Between one-eighth and one-fourth of all true neoplasms of the ovary are malignant. Therefore, it behooves us to beware of ovarian

neoplasia, benign or malignant. It would seem that the occasional discovery of symptomless ovarian tumors would justify periodic pelvic examination of all women 35 or more years of age.

Dr. Taylor states that "surgery remains the keystone of the treatment of carcinoma of the ovary." With this statement we must agree wholeheartedly. There would seem to be little question of how much tissue to remove in patients with lesions apparently confined to one or both ovaries. Nevertheless, only one in four of 185 patients with ovarian carcinoma recently reported from the Royal Victoria Maternity Hospital and the Department of Obstetrics and Gynecology of McGill University had bilateral salpingo-oophorectomy and total or subtotal hysterectomy. Recently Diddle traced 294 women with ovarian carcinoma treated in the City of Dallas during an eleven-year period ending Dec. 31, 1946. Only one in nine of them had adequate operation, if subtotal hysterectomy can be classed adequate. Otherwise, only seven women, or one in forty-two, received acceptable treatment.

Several important observations arose from Diddle's work: Ninety patients of this series were submitted to bilateral oophorectomy and more than one-half had histologically proved carcinoma in both ovaries. One-third of forty-six women submitted to hysterectomy had extension of the malignancy to the uterine wall or to the endometrium. One-seventh of 122 women with one or both Fallopian tubes removed had tubal metastasis.

It would seem, therefore, that the other ovary, the Fallopian tubes, and the uterus are involved with sufficient frequency to necessitate removal. Moreover in this day and age when total hysterectomy can be done with negligible mortality rates, it would seem that there could be no valid reason for allowing the cervix to remain during the course of any operation aiming at eradication of ovarian malignancy.

To sum this up, I believe that in general total hysterectomy and bilateral salpingo-oophorectomy should constitute the minimum acceptable surgical procedure for operable ovarian cancer.

The question of whether or not to administer postoperative irradiation has perplexed us all. Abdominal radiation carries an appreciable morbidity in terms of nausea, severe and prolonged anorexia, enteritis, and colitis. Occasionally death results from obstruction and fistula. For these reasons it is particularly gratifying to have Drs. Taylor and Munnell break down their figures in an attempt to clarify the problem and suggest that in some instances postoperative x-radiation is unnecessary.

DR. GEORGE KAMPERMAN, Detroit, Mich.—I would like to show one table which presents the all-over results at Harper Hospital since 1923.

HARPER HOSPITAL
FIVE-YEAR SURVIVALS OF CARCINOMA OF OVARY

	DEEP ROENTGEN THERAPY					DEEP ROENTGEN THERAPY					SUPER VOLTAGE ROENTGEN THERAPY			
	YEARS	CASES	WELL	PER CENT		YEARS	CASES	WELL	PER CENT		YEARS	CASES	WELL	PER CENT
A	1923	4	–	–	*C*	1933	15	2	13	*D*	1933	11	2	18
	1924	11	3	27		1934	10	1	10		1934	7	2	28
	1925	9	2	22		1935	9	1	11		1935	7	–	–
	1926	7	–	–		1936	1	1	100		1936	11	2	18
	1927	10	2	20		1937	1	1	100		1937	16	6	38
	Total	41	7	17		Total	36	6	17		Total	52	12	23
B	1928	14	3	21							1938	25	6	24
	1929	13	1	8							1939	13	6	46
	1930	11	4	36							1940	12	4	33
	1931	12	1	8										
	1932	12	3	15										
	Total	62	12	17							Total	50	16	32

It will be noted that the cases are grouped in groups of five years each. Groups A, B, and C show results for each five-year period as obtained by ordinary deep roentgen therapy (200,000 watts). It is significant that for each five-year period the total five-year survivals remained at 17 per cent.

Groups C and D were run parallel, during identical years. Group C was treated with ordinary deep roentgen therapy (200,000 watts), while those in Group D were treated with supervoltage roentgen therapy (600,000 watts). The five-year survivals went from 17 to 23 per cent when supervoltage roentgen therapy was used. Three additional years of supervoltage roentgen therapy are added and the five-year survivals for the entire group for supervoltage roentgen therapy is 32 per cent as compared with 17 per cent for the ordinary 200,000 volt deep therapy. We believe this is too significant to be ascribed to mere coincidence.

We believe that roentgen treatment cannot be too rashly pushed aside as a treatment for carcinoma of the ovary. As evidence of this we like to cite three cases which showed multiple general carcinomatoses, and were considered inoperable so far as a cure was concerned. Yet after roentgen treatment, one survived fourteen years without evidence of extension and finally died of a cerebral accident. Two other similar cases with general metastasis in the omentum, peritoneum, and in the intestines, are alive and apparently well six years and four years, respectively, after the operation and treatment, and today no evidence of disease can be demonstrated by physical examination. We believe that roentgen therapy has a definite place in the treatment of carcinoma of the ovary and we feel every patient should have the benefit of this.

In general, the treatment at Harper Hospital consists in the surgical removal of the primary lesion and the larger masses, with subsequent deep roentgen therapy. We believe surgical treatment is necessary and part of making the diagnosis. As a prophylactic measure we like to follow the suggestions of Crossen to remove both ovaries when operating on patients 44 years of age or over.

DR. E. D. PLASS, Iowa City, Ia.—Since we have recently made a preliminary study of our cases of ovarian carcinoma seen between Jan. 1, 1926, and Dec. 31, 1943, it seemed that the results might be of some interest. There were 267 patients with proved primary ovarian malignancies. The five-year control rate was 28 per cent with the greatest loss in the first and second years after therapy. Survivals beyond that period obviously become increasingly complicated by the attrition of age, the influence of which we have so far been unable to evaluate. When the average age at appearance of a malignant tumor is 55 years, it is to be expected that the ravages of the degenerative diseases of the aging will take a toll and thus complicate evaluation of any treatment of the malignancy.

The survival rate has also been studied in regard to the histologic type of the tumor. The high percentage of salvage in the group of cystadenocarcinoma brings into focus the difficulty of accurate histological evaluation which Dr. Taylor stressed. Does not this merely mean that attempts to determine functional cellular alterations, in this instance invasiveness, are likely to be inaccurate when reliance is placed upon examination of fixed and stained tissues? Experience in correlating these histological changes with the clinical course of the patient has been the basis of our attempts at evaluation, but it seems obvious that in borderline situations it is none too good.

The results have been studied of the various available therapeutic procedures used. Surgery with removal of as much as possible of the original growth together with extirpation of the remaining adnexa and the entire uterus has proved the most effective. Supplementary x-radiation, whether given before or after operation, added practically nothing to the control rate. Our efforts to provide radiation before surgical attack were discontinued after a few humiliating errors proved that we were unable to diagnose ovarian cancer clinically. Since then x-ray therapy has been concentrated in the early postoperative period. Our results certainly raise the question of whether such additional treatment is worth while. Those patients offered no treatment had such far-advanced lesions that exploratory laparotomy only was advisable with removal of tissue for histological study, and the Department of Radiology declined to treat these women.

Our incomplete statistical survey of this series does not yet permit comment upon the other problems introduced by Dr. Taylor. The similarity of our findings and final results does, however, emphasize that we are still far from attaining a satisfactory diagnostic and therapeutic attack upon ovarian cancer. Early diagnosis, which has been so effective in making possible the early treatment of external cancers, will likely be impossible in ovarian tumors until some blood or urine test is developed to show that the individual has a malignancy and thus to stimulate thorough search for its site. Let us hope that the investigations along this line now being so vigorously conducted will prove fruitful and thus provide us with a means of earlier diagnosis of all internal malignancies.

DR. EMIL NOVAK, Baltimore, Md.—The method of study employed by Dr. Taylor is an excellent one, and deserves emulation by others who will attack this problem in the future. There are, however, one or two points on which some issue may be taken. I do not know whether the authors are justified in making such a sharp differentiation between tumor type and cell differentiation factors, because they so commonly parallel each other. For example, a highly undifferentiated tumor is likely to be one in which the pattern is likely to be blotted out, so that, to give one illustration, it may be difficult to distinguish between a highly undifferentiated papillary cystadenocarcinoma and one of solid, medullary type.

More important, however, is the questionable justifiability of including in the classification of carcinomas certain cases which, from the slides which were shown, are clearly benign from a histological standpoint. It is beside the point to urge that in some cases of this type peritoneal implantation may occur, with the ultimate death of the patient. The same statement can be made of certain histologically benign pseudomucinous cystadenomas, which can bring about a histologically benign pseudomyxoma peritonei, with also ultimate death. Or it may be made of certain benign but locally invasive hydatidiform moles which may penetrate the uterine wall and occasionally cause fatal intra-abdominal hemorrhage. In other words, patients may die of histologically benign as well as histologically malignant ovarian tumors.

Since Dr. Taylor's otherwise excellent classification is a pathological and not a clinical one, it would seem that injection of the clinical consideration with one of his groups is like a mixing of metaphors. This is said with full appreciation of the fact that the papillary cystadenomas are as a group to be reviewed with more misgiving than the pseudomucinous, and that in an inevitable fraction of borderline cases pathologists will differ as to whether or not they are malignant. The first of the slides shown by Dr. Taylor, however, appeared to me not of this type, but definitely benign from a histological standpoint.

Finally, I would like to call attention to the fact that the sixteen cases of granulosa cell carcinoma in this series showed a survival rate of only 55 per cent, emphasizing a feeling I have long held that this tumor type is by no means to be taken as lightly as it is by some pathologists. This figure of 55 per cent would seem to me to be closer to the true one than the larger figure of 81 per cent survivals reported by Dr. Plass.

DR. LAWRENCE WHARTON, Baltimore, Md.—I should like to ask Dr. Taylor a question. Some time ago, I read a report of the very successful preoperative irradiation of inoperable ovarian carcinoma. This physician, however, reported three cases of large ovarian cancer which he operated upon but found inoperable. He did nothing but open and close the abdomen. In each instance, he followed the exploration by full roentgen therapy. The masses became much smaller, movable, and harder. The general condition of the patients improved. Eventually, he was able to remove these masses successfully. At the time of the report, these three patients had been well for eight to thirteen years since the operation.

I would like to ask Dr. Taylor whether he has had any such favorable experiences with irradiation in any of his cases of carcinoma of the ovary. I have had no such good results in my own experience, and the reports in the literature are not encouraging.

DR. WILLIAM P. HEALY, New York, N. Y.—I think it may be worth while to emphasize the value of postoperative irradiation in these cases of incompletely removed ovarian malignant tumors. There is a large series of ovarian tumors in which we did not consider

postoperative irradiation to be of value, such as in an encapsulated tumor mass in the borderline groups or in the adenoma malignum type of tumor in which you do total hysterectomy and bilateral salpingo-oophorectomy where there is nothing to suggest residual tumor growth. What would you irradiate there? Postoperative irradiation is not indicated in a case of that type, even if you do have a low-grade malignant tumor unless and until there is palpable tumor tissue present on subsequent follow-up examination. On the other hand, in other cases of malignant ovarian tumors where you are definitely unable to remove all the tumor tissue beyond any question of doubt, as indicated by Dr. Wharton's question, we have had in a limited number of cases very satisfactory response to postoperative irradiation in the way of prolonged life, not necessarily a five-year cure but prolongation. In the dysgerminoma group you are astounded at times at their remarkable response to roentgen irradiation in the way of total disappearance of extensive tumor masses. Those patients will live five or more years, so I think it would be very wrong to leave any impression that postoperative irradiation should not be utilized in an incompletely removed ovarian tumor.

DR. TAYLOR (Closing).—This discussion has emphasized the fact that if the results in carcinoma of the ovary are to be correlated with the various techniques of treatment, we cannot publish reports on total cures. Ovarian carcinoma is a group of diseases and not a single one. Although it is tempting to report the absolute cure rate for all cases of ovarian cancer, such a report is much less meaningful than five or six smaller reports on each of the divisions, each such study being based on a homogenous group of tumors.

Dr. Wharton asked about the apparent improvement after incomplete removal of ovarian carcinoma. While at Roosevelt Hospital I reported four cases in which operation was done and some but not all of the tumor was removed. Each case was either followed for ten to fifteen years or else reoperated upon for some other purpose. Spontaneous regression of the tumor was thus demonstrated. These four cases were, with regard to histology, of this borderline type.

I would like to defend two points which Dr. Novak attacked. First, he said that it was impossible to classify all types because when they became sufficiently undifferentiated no one can tell the type of cell they were derived from. That is absolutely true and in our tables there was one category for totally undifferentiated tumors. These tumors are, we believe, usually a form of extremely undifferentiated serous cystadenoma carcinoma, but the original characteristics of the cells are so lost that no one can say positively whether they were pseudomucinous or serous. You will always have a certain group of cases in which you cannot determine the histogenesis.

The other point is how to classify the case with borderline histology. Dr. Novak believes these are not histologically malignant and yet they may kill the patient. Here we may argue about the meaning of malignancy and whether structure or results define the word. I would prefer to study the life history of the tumor first and later decide from the life history what structure justifies the designation "malignant." There were nineteen cases in our borderline group among which the tumor recurred in two patients within five years and in three patients after longer intervals. This seems to me a fair demonstration of the biologically malignant quality of these tumors.

The major point, however, is to have some agreement on classification and I hope that we may soon develop a standardized system so that the results of different clinics may be compared with each other. We cannot do that if we continue to speak of total ovarian carcinomas and not of individual groups.

QUANTITATIVE STUDIES ON THE PRODUCTION, DESTRUCTION, AND ELIMINATION OF CHORIONIC GONADOTROPIN IN NORMAL PREGNANCY*

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THE study of endocrine patterns during normal and abnormal gestation is of both fundamental and practical importance. The present paper is concerned with a quantitative study of some aspects of the production and excretion of chorionic gonadotropin in normal pregnancy, and represents a summary of the work that has been carried out in our laboratory during the past two years.

Very early investigations[1-5] have shown that an active substance, now known as chorionic gonadotropin, is present in extracts of placenta, hydatidiform mole, and chorioepithelioma, and in the blood and urine of pregnant women. As is well known, it is the presence of this hormone in the body fluids of pregnant women that constitutes the basis for most biologic tests for pregnancy.[6-14] The origin of chorionic gonadotropin was at first erroneously ascribed to the anterior lobe of the pituitary gland, but later work,[15-22] especially the tissue culture techniques of Gey, Jones, Seegar, and Hellman, and others[23-25] established the trophoblast as being the source of this hormone. Its function in the human being has long been a matter of conjecture. Brown and Bradbury[26-28] have demonstrated that chorionic gonadotropin acts as a luteotrophic agent for the newly formed corpus luteum, but whether or not chorionic gonadotropin has any other function, particularly in the last two trimesters of gestation, is unknown. The concentration of hormone in the blood and its urinary excretion in normal pregnancy have been studied quite extensively.[29-32] A rather characteristic pattern is present, consisting of a rise in both serum concentration and urinary excretion between the fiftieth and seventieth days of pregnancy, and a fall to a lower, constant level for the remainder of pregnancy. The hormone disappears from both blood and urine within a few days after delivery.

Despite these investigations, there is still a dearth of information concerning the normal values of serum chorionic gonadotropin. This unfortunate situation is due to the fact that many workers have used assay methods which have only local significance, since no two assay methods can be expected to yield identical results. The data of Delfs and Jones,[33] Rubin, Dorfman, and Miller,[34] and Gastineau, Albert, and Randall[35] are exceptional in that they are presented in terms of International Units, but they comprise less than fifty cases in all. Because of the recent importance[36-42] attached to abnormal hormonal values in toxemia of pregnancy, it seemed worth while to obtain a sufficient series of normal values in terms of International Units, so that results of different labora-

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tories could be readily compared, and so that any single determination could be satisfactorily classified as normal or abnormal. The first phase of our work has therefore been directed toward the establishment of normal values in terms of an absolute and universal standard of measurement in a sizable population of normal pregnant women.

The second phase of our work has been directed toward an analysis of the factors which might determine the characteristic pattern of the fluctuations in chorionic gonadotropin during normal pregnancy. It is fairly obvious that the amount of hormone present in serum at any given time must represent the difference between the amount produced during that time, and the sum total of all metabolic processes that might inactivate the hormone, utilize it, and eliminate it from the body during that time. For example, does the peak in serum and urine which occurs between the fiftieth and seventieth days represent an increased production of the hormone, or a decrease in either renal elimination or destruction? Does the lower urinary elimination during the last two trimesters indicate an altered renal function with respect to this hormone? Again, the recent importance attached to the utilization theory of this hormone in abnormal states makes it highly desirable to learn what factors determine the normal patterns of excretion. Any concept of the role of this hormone in abnormal states of pregnancy could be considered as only tentative until as many factors as might influence the level of this hormone in normal pregnancy could be delineated. Consequently, we have attempted to resolve the relative importance of such factors as production and excretion (renal and extrarenal) on the normal fluctuations of this hormone.

Material and Methods

Approximately 132 normal pregnant women furnished the basis for our studies. These were patients routinely seen and followed in the Section on Obstetrics and Gynecology of the Mayo Clinic. Venous blood and twenty-four-hour collections of urine were obtained from these patients at various intervals of pregnancy and during the immediate post-partum period. Chorionic gonadotropin was determined by the method of Albert.[43] Briefly, this method utilizes ovarian hyperemia as an end point, and consists in determining the median effective dose by serial dilution of either blood or urine. Since the median effective dose is 1 I.U., the amount of hormone in International Units per cubic centimeter can readily be calculated by the dilution factor, and in turn for the entire circulating serum or twenty-four-hour urine specimen. The chief advantage of this method is its speed and convenience, thus permitting work on an extended basis. Its over-all accuracy is ± 30 per cent.

Results

A. *Level of Chorionic Gonadotropin During Normal Pregnancy.*—The results of single determinations in 112 normal pregnant subjects are shown in Fig. 1. No attempt was made to follow any of these patients serially, since this has already been studied by Delfs and Jones[33] and also by Gastineau, Albert, and Randall.[35] The use of single determinations in many patients seemed to us to have more clinical significance than serial determinations in a few patients, for it allows a better view of the extent of variation in entirely normal pregnant subjects.

The shape of the curve as indicated by plotting the mean values indicates a peak level in concentration of hormone occurring about the fifty-fifth day after the last menses. A gradual reduction occurs, so that from the hundredth day until parturition a fairly steady level of about 20 I. U. per cubic centimeter of serum is present. These values are in good agreement with those reported by others.[33]

The establishment of a sufficient number of normal determinations makes it possible to study the role of chorionic gonadotropin in abnormal states, particularly the toxemias. This is of prime clinical importance, since there is some controversy as to the behavior of this hormone in toxemia. The Smiths[36-42] have pointed out that a rise in serum gonadotropin occurs four to six weeks prior to the appearance of toxemic symptoms, and White and her associates[44-48] have attached great significance to this finding in terms of therapy. However, Taylor and Scadron[49] have been unable to confirm this rise in serum gonadotropin. Rubin, Dorfman, and Miller[34] studied intensively five cases of diabetes associated with pregnancy. In two of three patients who had no signs of toxemia the serum gonadotropin levels were normal, and in the third patient the levels were significantly increased. Of two patients with clinical signs of toxemia, one patient with mild toxemia had normal levels of chorionic gonadotropin and the other, with severe toxemia, had significantly increased levels of gonadotropin. It appears then that there is some uncertainty concerning the significance of abnormally high levels of serum gonadotropin in toxemia. The establishment of our series of normal values will therefore be of great use in determining abnormal levels in toxemia, a study that is now in progress.

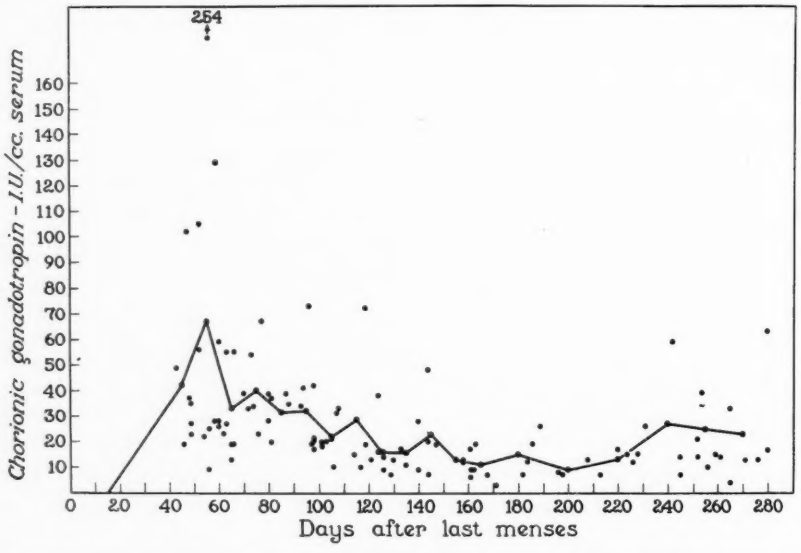

Fig. 1.—Concentration of serum chorionic gonadotropin in 112 subjects during normal pregnancy.

B. *Factors Influencing the Characteristic Pattern of Chorionic Gonadotropin in Blood and Urine.*—As was pointed out previously, the level of hormone in serum and urine may be the resultant of many factors. In the opinion of Browne, Henry, and Venning[29, 30] the peak excretion reflects a physiologic necessity in order that the function of the corpus luteum in early pregnancy may be maintained. Additional support to the concept of increased production has come from the histologic studies,[21-25] which indicate a direct proportionality

between the number of Langhans' cells and the amount of hormone eliminated. On the other hand, Smith and Smith[42] have emphasized that the production and utilization of hormone are regulated by the steroids produced during pregnancy.

However, the role of the kidneys has never been evaluated satisfactorily. Since it is possible that changes in renal function during pregnancy would lead to changes in the concentration of hormone in the serum, renal function with respect to chorionic gonadotropin was studied by Gastineau, Albert, and Randall.[35] Five normal patients were observed throughout pregnancy and the renal clearance of chorionic gonadotropin was determined. An example of this study is given in Fig. 2. The clearance of hormone (that is, the volume of blood cleared of chorionic gonadotropin per minute) was found to remain constant at a level of about 0.38 c.c. per minute throughout pregnancy, despite the fact that the concentration of hormone in the blood was much higher in the first trimester than in the last two trimesters. Thus, the characteristic hormonal pattern is not due to changes in renal function during normal pregnancy. The possibility still remains, however, that in abnormal pregnancy such as toxemia, the rise in serum levels could result from altered renal function. The study of renal clearance of hormone in these states would furnish such much-needed evidence.

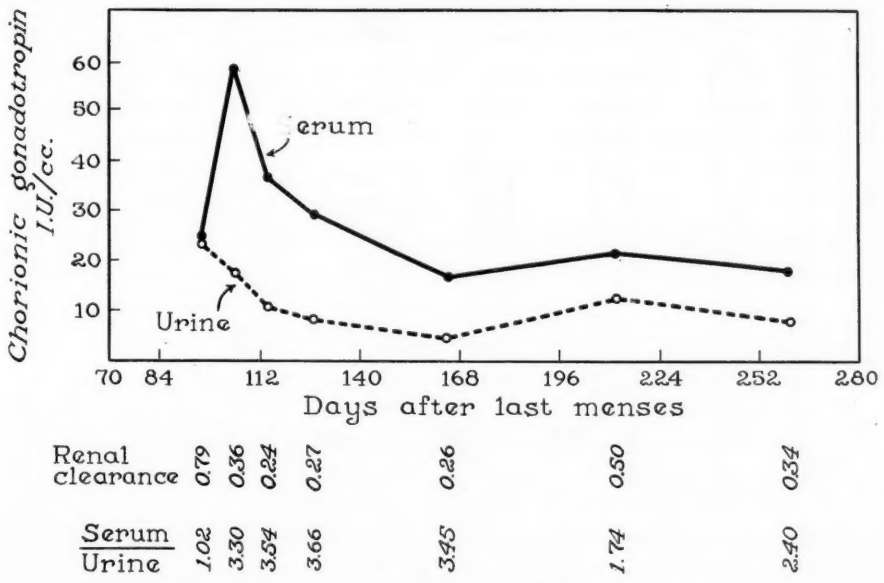

Fig. 2.—Simultaneous serial assays for chorionic gonadotropin in a normal pregnancy, with renal clearances and serum-urine ratios.

Clearance: The volume of plasma, in cubic centimeters, containing the same amount of substance as is found in one minute's urine.

Example 1. Clearance:

$$\frac{\text{30,300 (I.U. chorionic gonadotropin in 24-hour urine)}}{\text{1,440 (number of minutes in 24 hours)}} = \text{21 I.U. in 1 minute's urine}$$

$$\frac{\text{21 (I.U. chorionic gonadotropin in 1 minute's urine)}}{\text{58.7 (I.U. chorionic gonadotropin in 1 c.c. of serum)}} = \text{0.36=renal clearance}$$

Example 2. Ratio:

$$\frac{\text{58.7 (I.U. chorionic gonadotropin in 1 c.c. of serum)}}{\text{17.8 (I.U. chorionic gonadotropin in 1 c.c. of urine)}} = \text{3.30=serum-urine ratio}$$

Since the renal elimination of hormone cannot account for the hormonal pattern, the remaining two possibilities—changing production and changing utilization (or destruction, or extrarenal disposal)—were investigated. It is difficult to determine the rate of production directly by experimental or other means. However, an indirect estimation of this factor could be obtained if it were possible to determine how much hormone was disposed of by all processes other than renal elimination. Such processes would represent the total of endogenous destruction, utilization or excretion by routes other than the kidneys. Such an estimation is also difficult to obtain directly, since a direct experimental solution would involve the injection of chorionic gonadotropin during pregnancy and the measurement of its fate, distribution, and excretion. Since, in pregnancy, endogenous hormone is being produced, perhaps at a variable daily rate, the results of such determination would be fraught with some uncertainty. The use of nonpregnant patients in studies of this sort has therefore been resorted to by others, but it is to be recalled that the results of such investigations are not necessarily applicable to the pregnant subject.

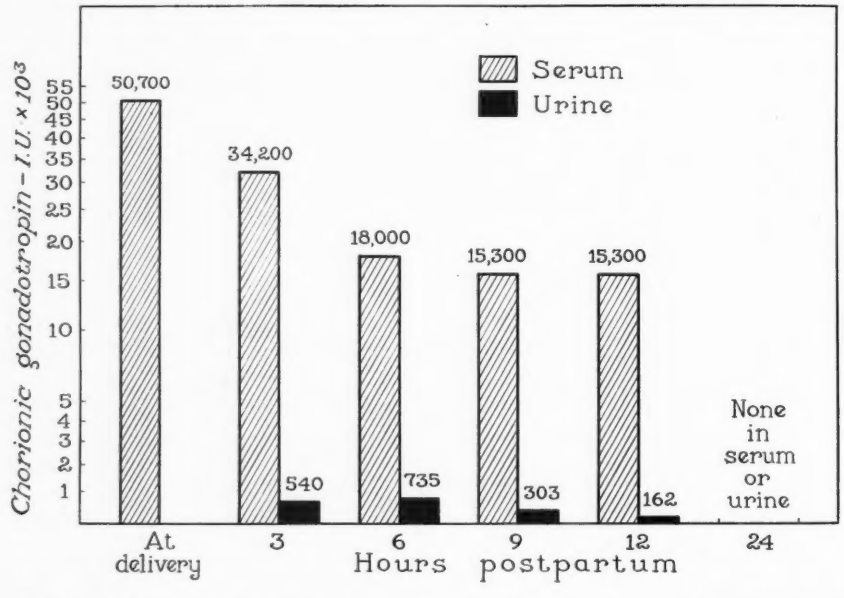

Fig. 3.—Total chorionic gonadotropin in serum and urine at various intervals after delivery.

As a compromise approach, the following attack was chosen by Johnson, Albert, and Wilson.[50] The concentration of hormone in serum was determined at the time of delivery in fifteen normal pregnant women, and also in all of the urine excreted after delivery. From these values, the total amount in the circulating blood serum can be estimated as the product of the concentration of hormone in serum and the total volume of serum, estimated at 5 per cent of body weight or approximately 3 liters. The total amount of the hormone appearing in the urine was determined directly. If all of the serum hormone appeared in the urine, then it would seem that none of it was disposed of elsewhere, or destroyed or utilized. The results of this study, an example of which is shown in Fig. 3, indicate that only 6 per cent of the hormone in the serum appears in

the urine. The remaining 94 per cent must therefore be destroyed, utilized, or disposed of by other means, since the production of the hormone has ceased, owing to the removal of the placenta.

The estimation of extrarenal disposal of circulating hormone to the extent of 94 per cent is in excellent agreement with the results obtained by Zondek and Sulman[51] in animals. They have found that only 5 to 10 per cent of injected hormone appears in the urine, and that a large portion of the remainder is destroyed by tissues of the body. However, our estimations are at variance with the work of Bradbury and Brown,[52] who stated that relatively little destruction or utilization of the hormone occurs in the human being (nonpregnant women). Whether this discrepancy is due to differences in method or interpretation, or to a difference in behavior of nonpregnant subjects as opposed to those just delivered remains to be determined.

At any rate, it seems reasonable to regard the characteristic hormonal pattern as resulting from changes in the rate of production, since the renal disposal remains constant throughout pregnancy, and since there is no valid reason to suppose that the extrarenal disposal varies during pregnancy. This view, which is supported for the first time by direct and indirect experimental data, is in agreement with the opinion expressed earlier by Browne and Venning,[29] and by Wislocki, Dempsey, and Fawcett[22] on the basis of histologic methods.

Summary

The levels of chorionic serum gonadotropin in normal pregnancy have been determined in 112 patients in terms of International Units. A characteristic curve for this hormone has been obtained, agreeing in both pattern and absolute values with those reported by others. An analysis of the factors which might influence the characteristic hormonal pattern indicates that the renal function with respect to the hormone remains constant during normal pregnancy, that the extrarenal disposal of the hormone accounts for more than 90 per cent of the circulating hormone, and that probably the fluctuating character of hormonal level in serum or urine depends entirely on changes in rates of production of hormone during pregnancy.

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Discussion

DR. WILLARD M. ALLEN, St. Louis, Mo.—There are several points in Dr. Randall's paper which are of unusual interest.

I wonder if the levels of chorionic gonadotropin which are supposedly uniformly high in early pregnancy are really as high as we suppose. In his studies there are numerous observations at about the fiftieth day after the last menstrual period which do not seem to be so very much greater than observations made at much later stages of pregnancy.

The rate of disappearance of the hormone after delivery of the placenta is very revealing. He finds that only 10 per cent of the amount of hormone estimated to be present in the serum at the time of delivery ever finds its way into the urine following delivery. This correlates very well with other studies on the excretion of sex steroids. Studies of that type usually show that approximately 10 per cent of the injected material appears in the urine. What happens to the other 90 per cent?

The liver is considered to be the organ responsible for the inactivation of the sex steroids. Is it also the organ responsible for the destruction of chorionic gonadotropin?

We will anxiously await his studies on renal clearance of chorionic gonadotropin in the toxemias now that the basic work on normal pregnancies has been done.

DR. GEORGE VAN S. SMITH, Brookline, Mass.—Dr. Randall's paper raises many questions. It was gratifying to see that the curve of chorionic gonadotropin he presented is almost exactly similar to the curve we were the first to publish in 1936, based on the simple Aschheim-Zondek method.

I would like to ask Dr. Randall if he can offer any explanation for the finding of high chorionic gonadotropin preliminary to the development of toxemia of pregnancy.

DR. OLIVE SMITH, Brookline, Mass. (by invitation).—One important point in the curve Dr. Randall presented was that it confirmed our finding of a tendency for chorionic gonadotropin to rise at the termination of normal pregnancy. I wonder if there is any evidence for increased production at the end of pregnancy?

DR. GEORGIANNA JONES, Baltimore, Md. (by invitation).—I would like to say a few words about the chorionic gonadotropic assays which we have done. We have reported twenty-five normal patients with assays weekly throughout pregnancy. In addition, we have studied approximately fifty patients with abnormal reproductive histories who have gone through pregnancy normally and twenty-five or thirty patients who have aborted. As Dr. Smith has said, it is gratifying to know that the curves done in almost all the laboratories throughout the country are fairly similar. I think there is very little doubt that the rise in chorionic gonadotropic titer at about the sixtieth day does occur in normal pregnancy consistently. We have never studied a normal pregnancy or a pregnancy that went to term in which the titer has not risen to at least 40,000 I.U. per liter from a level of 2,000 to 3,000. It is certainly true also that around the 210th day in normal pregnancy there is a secondary elevation. In our cases, instead of rising from 40,000 to 100,000 I.U. as it does at the fiftieth to sixtieth day of pregnancy, the titer seldom goes above 20,000 and I believe our highest normal case was 30,000 I.U. per liter. In our experiences these values usually drop before delivery. It would be desirable to have an explanation of this rise, but I would like to point out that such a rise late in normal pregnancy makes the interpretation of a rise in abnormal pregnancy very difficult.

DR. RANDALL (Closing).—It is evident by this brief paper and its discussion that what we have presented here today represents an exploration into a complicated field.

Dr. Smith asks a very pertinent question. I would like to be able to answer it: whether this renal clearance would answer the question of why high levels occur, I do not know. In exploring this field, and we feel it is very important, we have to date stayed away from abnormal pregnancies. It has been pointed out that until we had sufficient experience in the normal pregnancy we had no right to explore the abnormal field. We believe now we have advanced to the state where we can examine excretion of the hormones in abnormal pregnancies and I hope to be able to report on this later.

In this matter of the end of pregnancy rise we have felt perhaps it was not sufficient to be significant. I do not know that that is a very safe statement to make but as we have plotted them in the last part of pregnancy we have felt there is no significant rise, but now I believe there is and its significance makes one pause a bit. If there is a rise in both abnormal and normal pregnancy I will be unhappy because I think it would be easier to explain a perfectly flat curve.

A SERIES OF POTENTIALLY ABORTIVE OVA RECOVERED FROM FERTILE WOMEN PRIOR TO THE FIRST MISSED MENSTRUAL PERIOD*

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Introduction

IT IS the purpose of this paper to present some observations which may throw light on the etiology and pathogenesis of spontaneous abortion. Since the latter occurs in approximately 10 per cent of patients who are clinically pregnant and undoubtedly is present, but unrecognized, in some patients complaining of sterility, the relationship of this subject to infertility is obvious.

In the past there have been two schools of thought with regard to the etiology of spontaneous abortion. The late Dr. Mall[1] believed that an abnormal uterine environment was responsible for this ovular wastage. On the other hand, the late Dr. Streeter[2] and his group believe that there is something intrinsically wrong with the fertilized ovum itself—expressed by the general term of "germ plasm defect"—rather than with the maternal environment.

Material

During the past ten years, from November, 1938, to October, 1948, Dr. Rock and I have been studying at the Free Hospital for Women various aspects of human reproductive physiology and pathology. Within this period of time we have discovered twenty-eight early human conceptuses in uteri removed therapeutically for a variety of reasons. None of the patients had missed their next expected menstrual period so that these specimens are younger than sixteen days of age.

The 136 cases,† which comprise the study group from which these specimens were obtained, are a special group of fertile patients in whom pregnancies might occur. Indeed they had averaged nearly five normal pregnancies per patient. A preliminary report on the smaller series then extant was made in 1942 before

*Paper presented by Dr. Hertig. This study has been aided by grants from the Carnegie Corporation of New York and the William F. Milton Fund of Harvard University. It has been read, in part, before the Conference on Menstruation and Its Disorders, January, 1947, New York City. Permission to reprint parts of the text and illustrations has been generously granted by Charles C Thomas, Publisher, publisher of the proceedings of that conference.

†Since October, 1948, eleven additional uteri have been searched for early conceptuses, three of which have been found. They are not included in this series since none have been completely studied although two free-lying segmenting forms are briefly mentioned in the text to illustrate a normal 4½-day blastula (Fig. 1) and an abnormal five-cell morula (Fig. 3).

this Society by Rock and Hertig.[3] The finding of twenty-eight early pregnancies in the present series of 136 potentially pregnant patients thus gives us a fertility index of 20.6 per cent. To be sure, these patients are naturally past their reproductive prime since as a group they are older and, moreover, have come to a gynecological clinic for a variety of complaints. Nevertheless, to our knowledge, this is the only recorded index of human fertility in a group of

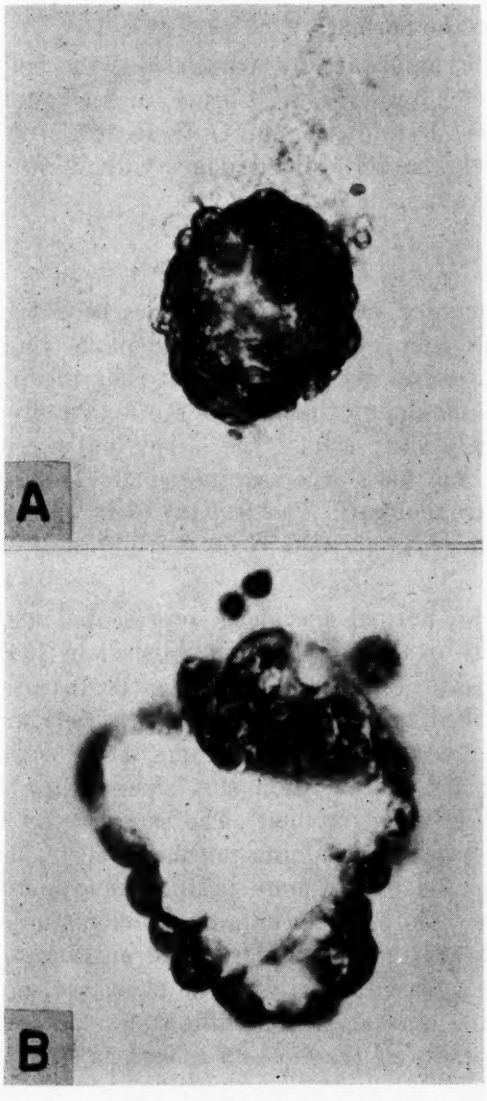

Fig. 1.—A normal human blastula of approximately 4½ days of age recovered from the uterine cavity on the nineteenth day of the menstrual cycle. Carnegie No. 8663.

A, Intact blastula after fixation and partial dehydration. The segmentation cavity and variation in thickness of the wall is readily made out. Sequence 3 × 300.

B, A cross section of the blastula taken to include a significant diameter of the embryonic mass. The latter, composed of larger cells, is in the upper portion of the picture. The smaller cells composing the wall of the blastula are destined to become trophoblast and hence form the chorion. The prominent segmentation cavity, in the center of the blastula, is thus destined to form the chorionic cavity. Note two maternal cells, one a polymorphonuclear leucocyte, above the embryo which give some idea of the relative size of the blastula and its component cells. Section 6 × 600.

known fertile women who have recorded coital data during the probable ovulation time of any one menstrual cycle.

Of the twenty-eight early pregnancies obtained, twelve were interpreted by Drs. Streeter, Corner, and ourselves as being abnormal in one way or another. Ten of these specimens will be described and illustrated in some detail within the text. For comparative purposes, a normal blastula as well as a previllous and early villous ovum will also be described so that you may see wherein the abnormal differs from the normal.

It is my pleasure, as always, to acknowledge the help and cooperation of Drs. George L. Streeter,* George W. Corner, and Chester H. Heuser, Messrs. Chester Reather, James F. Didusch, and O. O. Heard, Mrs. Miriam Menkin, and the Misses Susan Hedge and Eleanor Adams, without whose various skills this material would not be available for study.

I. Normal Ova

Although not included in the present series because of incomplete study, Fig. 1 illustrates the youngest normal human ovum thus far observed. The blastula was found free in the uterine cavity on the nineteenth day of the menstrual cycle. Its maximum diameter is approximately 130 μ and it is composed of approximately sixty cells. The larger and eccentrically located ones represent the embryonic mass whereas the smaller peripheral lying ones are to form the future trophoblast. The general form of the specimen is seen in Fig. 1,A while the microscopic details of the mid-sagittal section are seen in Fig. 1,B.

In Fig. 2 are two normal specimens represented merely for comparative purposes. The 12-day ovum, previously published in 1941,[4] is represented by a mid-cross section seen in Fig. 2,A. Its essential features are clearly evident and are briefly described as follows: The ovum is well implanted although not as yet completely covered by the endometrium. The normal late secretory endometrium, comprising the implantation site, shows a moderate predecidual reaction of the stroma about the ovum. The serrated, secretorily active glands contain inspissated glycogen-containing mucus. The trophoblast, or outer shell of the ovum, is composed of the more peripheral syncytiotrophoblast and the inner cytotrophoblast. The former contains intercommunicating lacunae within which is maternal blood, whereas the latter are proliferating in masses to form the future chorionic (placental) villi. The chorionic cavity is the most conspicuous feature of the normal ovum at this stage and is the lineal descendant of the segmentation cavity of the blastula as seen in Fig. 1. (It may be absent as will be noted (Fig. 5) in one of the pathological specimens.) The cavity is lined by an imperfect membrane originally described in the monkey by Heuser in 1932.[5] It is continuous with the primitive entoderm of the germ or embryonic disc. The latter also possesses primitive ectoderm and is thus double layered. A primitive amnion, attached to the edge of the ectoderm, is also present at this stage.

*Deceased, July, 1948.

The 16-day stage, represented by a normal early villous specimen, is seen in mid-cross section in Fig. 2,B. Its histological details are less evident than in the younger specimen because its much larger size makes a smaller magnification necessary. However, the interstitial type of implantation is now evident since the ovum is fairly well covered by regenerating endometrium. The early compact decidual reaction of the endometrial stroma about the ovum is easily seen. The most conspicuous feature of the ovum itself is the presence of early branched

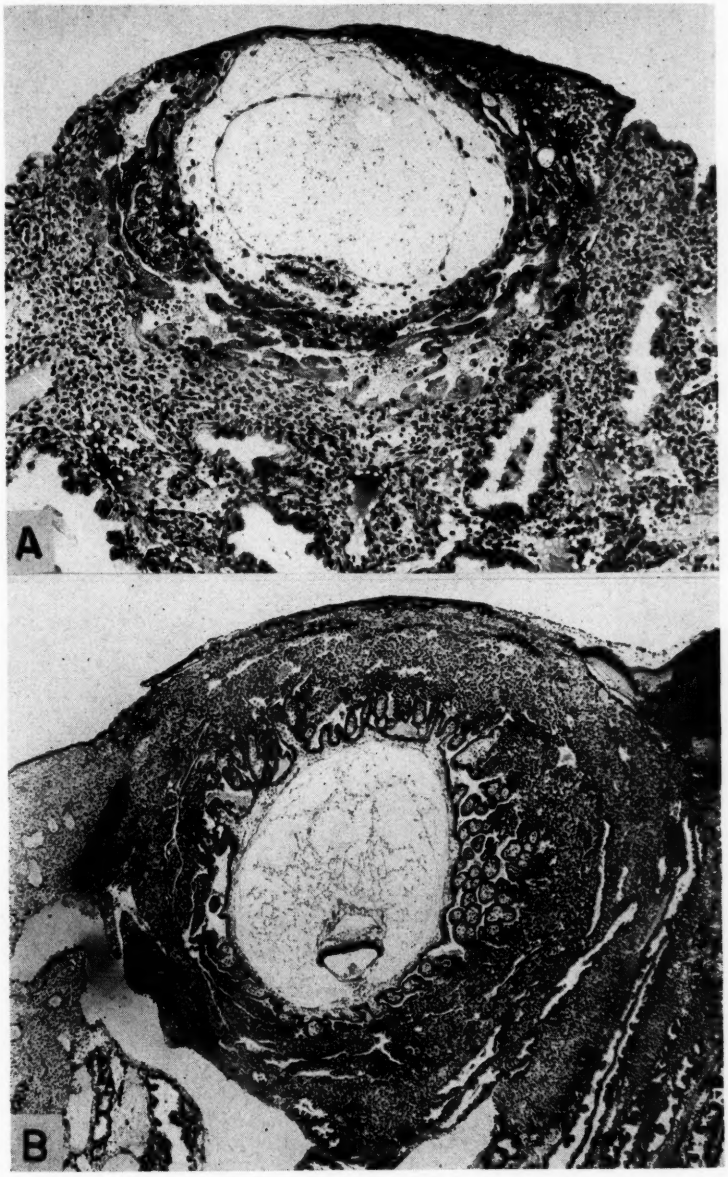

Fig. 2.—A, A normal 12-day human ovum shown in mid-cross section. Carnegie No. 7700, section 5-7-7 × 100.

B, A normal 16-day human ovum shown in mid-cross section. Carnegie No. 7802, section 44-3-5 × 30.

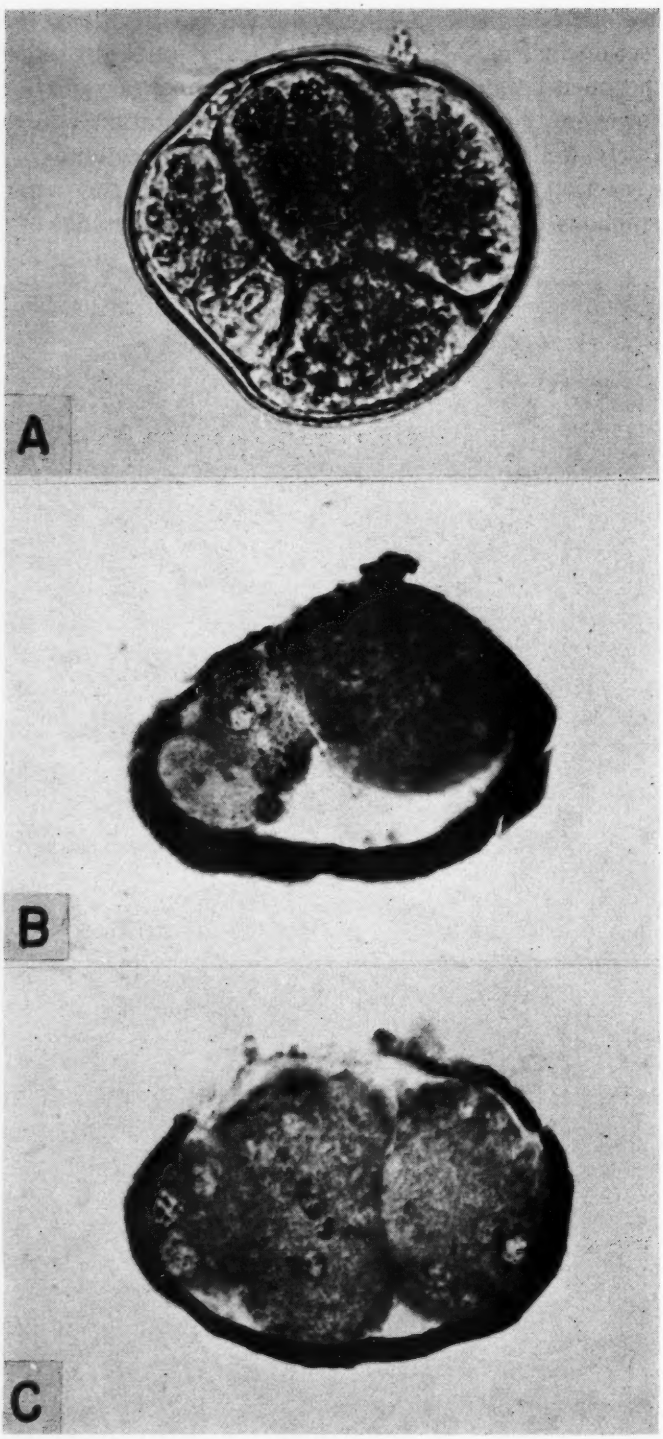

Fig. 3.—A five-cell abnormal human morula of approximately 4½ days of age. (Compare with Fig. 1, a normal specimen of comparable age.) Carnegie No. 8630.

A, Intact specimen after fixation and partial dehydration. Note variation in size of blastomeres most of which contain two or more nuclei. Sequence 7 × 500.

B, A parasagittal section to show variation in size of blastomeres, poor staining quality of cytoplasm, annd multiplicity of nuclei. Section 6 × 600.

C, A mid-sagittal section to show portions of three blastomeres whose cell boundaries are indistinct, their cytoplasm muddy and nuclei multiple. Section 10 × 600.

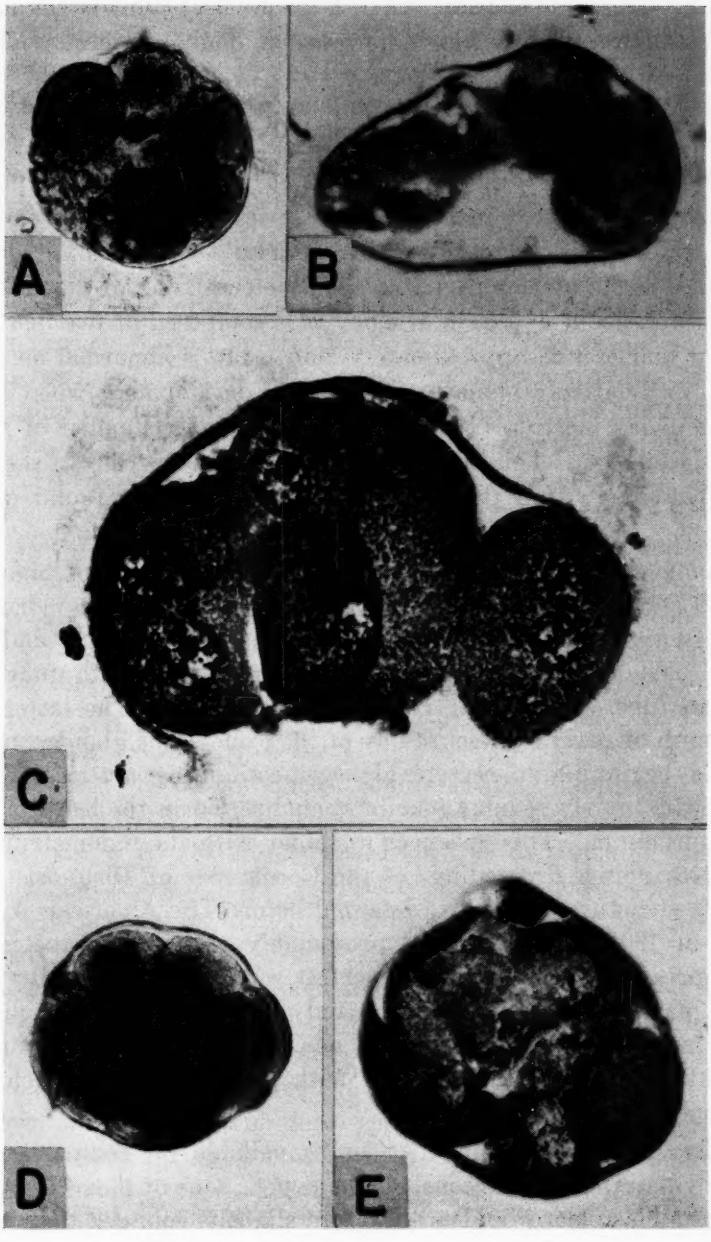

Fig. 4.—Three abnormal human morulas of approximately 3½ to 4 days of age recovered from the uterine cavity. A and B show an eight-cell specimen, Carnegie No. 8450. C shows a nine-cell specimen, Carnegie No. 8190. D and E show a twelve-cell specimen, Carnegie No. 8452.

A, Intact specimen shown by transmitted light. Sequence 7 × 300.

B, Mid-cross section to show the flattening of the morula and the degenerative nuclear changes in two of the four blastomeres. Section 8 × 500.

C, A section through the greatest diameter of the specimen to show the oval outline of the morula and six of its blastomeres, some of which are multinucleated. Section 8 × 600.

D, Intact specimen viewed by transmitted light. Sequence 2 × 300.

E, One of serial sections through the greatest diameter of the specimen to show the variable size, shape, and staining reaction of the various blastomeres. Note double nucleus toward 6 o'clock. The nuclei in general are not distinctly outlined nor are the individual blastomeres clearly demarcated. Section 8 × 500.

chorionic villi. The large chorionic cavity, lined with primitive connective tissue, contains an embryonic disc which now has a double layered yolk-sac and a definitive amnion.

II. Abnormal Ova

1. *Segmenting, Free in the Uterine Cavity.*—

Although not included in the present series because of incomplete study, Fig. 3 illustrates the youngest abnormal human ovum thus far observed. It was found free in the uterine cavity on the nineteenth day of the menstrual cycle and is, therefore, about 4½ days of age. It is composed of five blastomeres and its maximum diameter is approximately 200 μ. It is abnormal on at least two counts: (1) its relatively immature embryonic development when compared to the normal 4½-day blastula (Fig. 1) and (2) the large number of nuclei in the individual blastomeres. This multiplicity of nuclei in the cells of the segmenting ovum has characterized all the other abnormal free forms found in this study (Fig. 4).

The youngest completely studied specimen in the present abnormal series is a nine-cell segmenting ovum (Fig. 4,C) recovered as a free morula from the uterine cavity approximately three to four days after ovulation and subsequent fertilization. The associated active recent corpus luteum with unhealed stigma, the Fallopian tube, and endometrium were all normal. The latter was in the late seventeenth or early eighteenth day of the cycle. The glands were markedly tortuous and beginning to secrete glycogen-containing mucus. This was apparent as a wide, fairly regular zone of vacuolization in the basal portion of the glandular epithelium. This specimen together with its endometrium was published in 1946[6] in the Proceedings of the Conference of Diagnosis in Sterility. Details of its structure were also presented before The American Association of Anatomists in 1946.[7] Its oval and presumably abnormal shape is evident in Fig. 4,C, representing one of fifteen perfect serial sections cut by Dr. Heuser. Of the nine blastomeres in the specimen, only five contain a single nucleus, three contain two nuclei, while the remaining one possesses three. It is the presence of these multinucleated cells, together with its oval shape, which makes this specimen appear to be abnormal.

Two other segmenting human ova are available for comparison in Fig. 4, although they have not been reconstructed as yet. One of them, Figs. 4,A and B, has only eight blastomeres and is therefore slightly younger than the previous specimen. Two of the blastomeres are beginning to undergo necrosis (Fig. 4,B) whereas at least one of the viable cells possesses two nuclei (Fig. 4,A). Furthermore, it is flattened in one plane although circular in the other. Thus it is probably abnormal though it confirms the fact that the eight- to nine-cell human ovum is present as a free morula in the uterine cavity by the eighteenth day of the menstrual cycle. The endometrium, as in the nine-cell specimen, was perfectly normal.

The third segmenting specimen, also probably abnormal although somewhat more normal than the two others, has approximately twelve blastomeres (Fig.

4,D and E). It is about 4 days of age and was associated with normal eighteenth-day secretory endometrium. It is spherical and the majority of the cells contain only one nucleus each. Furthermore, some of the blastomeres are beginning to show variation in size, shape, and staining reaction. This probably represents early differentiation of trophoblastic cells as compared to those of the definitive embryo. Such a process has been described by Heuser and Streeter for the domestic sow in 1929.[8]

Even though detailed studies on two of the three segmenting ova available in the present series are not complete, it is evident that abnormality at this stage of human development is relatively common. That this should be so follows from Corner's[9] work on the domestic sow. This author showed that of 100 ovulated eggs, only 70 per cent possessed enough normality to reach term. Of the remaining 30 per cent one-third, or 10 per cent, failed to become fertilized even though exposed to spermatozoa, one-third segmented but failed to implant, while the residual one-third implanted but aborted before the fetus reached viability.

It is obvious that patients complaining of sterility may fall into the first two groups, whereas the occasional and/or habitual aborter coincides with the last group. It is interesting that this figure of 10 per cent (one-third of 30 per cent) implanted ova of the domestic sow which are destined to abort is quite comparable to the 10 per cent incidence of spontaneous abortion in the human species.

2. *Ovum With Trophoblast Only.*—

This specimen (Fig. 5) is the most abnormal of any implanted human ovum thus far observed. It is characterized by the complete lack of an embryo or chorionic cavity. Even its trophoblastic shell is defective in that the inner cytotrophoblast is absent. The syncytiotrophoblast, however, is present and seems relatively normal in that it invades endometrium, forms lacunae, and erodes maternal blood vessels.

An abnormal ovum was suspected from the appearance of the gross specimen because of the flattening and radial wrinkling of the implantation site (Fig. 5,A). Whether the ovum was better organized and had had more of its normal component parts at some previous stage of development is impossible to say. It seems unlikely, however, that in the segmenting stage any cavity or embryonic cell had been present. It has been shown by Heuser and Streeter in 1941[10] that the syncytiotrophoblast is the first definitive type of trophoblast to form at the embryonic pole after the monkey blastocyst implants on the endometrium, it forming from indifferent polar trophoblast nearest the maternal endometrium. It may be this factor of maternal contact which causes one indifferent trophoblastic cell to become syncytial in type whereas the lack of such maternal environment results in primitive trophoblast forming cytotrophoblast. Whatever the factor responsible, syncytiotrophoblast is the first recognizably differentiated form of trophoblast seen at the implantation pole of the ovum.

What the sequence of events is for the human being at this stage of implantation is unknown. However, the youngest implanted human ovum thus far studied (Hertig and Rock, 1945[11]) shows a transition from the thin meso-

thelium-like trophoblast at the embryonic pole to an indifferent stage at the equator of the ovum where the latter has contact with maternal tissue. (Thus, this part of the 7½-day ovum may be quite comparable to the embryonic pole of an implanting blastocyst soon after attachment to the endometrium.)

Since syncytiotrophoblast is apparently only slightly less primitive than the indifferent variety, it may be postulated that this very abnormal ovum possessed only this relatively limited ability to differentiate. The lack of cytotrophoblast or embryo, and more particularly a chorionic cavity, would tend to indicate that the preimplantation form of this ovum consisted of merely a few primitive trophoblastic cells that had the potential for forming syncytiotrophoblast only.

It is impossible to give the developmental age of this specimen although the clinical history and endometrial picture suggest approximately 11 to 12 days. The endometrium is perfectly normal and in the twenty-sixth day of the menstrual cycle. The moderate progestational hyperplasia, consisting of increased secretion and persistent stromal edema, is undoubtedly due to the pregnancy and its direct or indirect effect on the corpus luteum since all pregnant endometrium of this stage shows these features. The hemorrhage within the gland (Fig. 5,B) is within normal limits since it is present in the implantation site of normal early villous pregnancies of 13 to 16 days of age. It is due to the encroachment of the growing trophoblast upon the adjacent glands at a time when the uteroplacental circulation is becoming established.

Whether this pregnancy would have caused the patient to miss her next menstrual period it is impossible to say. The probable resulting lack of chorionic gonadotropic hormone, stemming from lack of cytotrophoblast, makes it unlikely that this patient would have missed her next expected menstrual period. It seems unlikely, however, that were amenorrhea to ensue it would have lasted for more than a few days to a week. In all probability, the patient would then have had a profuse, albeit a somewhat delayed, period but with no definite clinical evidence of pregnancy. Thus this patient, were she a clinical problem, would fall into the ill-defined zone between sterility and infertility. It is interesting to note that in her own obstetrical history she had had five normal children with no abortions. Hence even apparently perfectly fertile patients have their "germ plasm defects" on occasions even though relatively young (31 years of age).

3. *Ovum Without Embryo.*—

This specimen (Fig. 6) represents the most common clinical type of pathologic or "blighted" ovum encountered in obstetric practice. Since "blighted" ova, in general, constitute about half of all abortuses examined at the Boston Lying-in Hospital,[12] the present specimen is representative of about 5 per cent of all clinical pregnancies. These abnormal pregnancies tend to abort at about 10 weeks (menstrual age) and often show early hydatidiform degeneration of their villi.[13]

The essential gross features of the specimen are seen in Fig. 6,A and the microscopic details in Fig. 6,B. This ovum, together with those shown in Figs. 8 and 10,B have been previously published.[14] The ovum possessed a polypoid

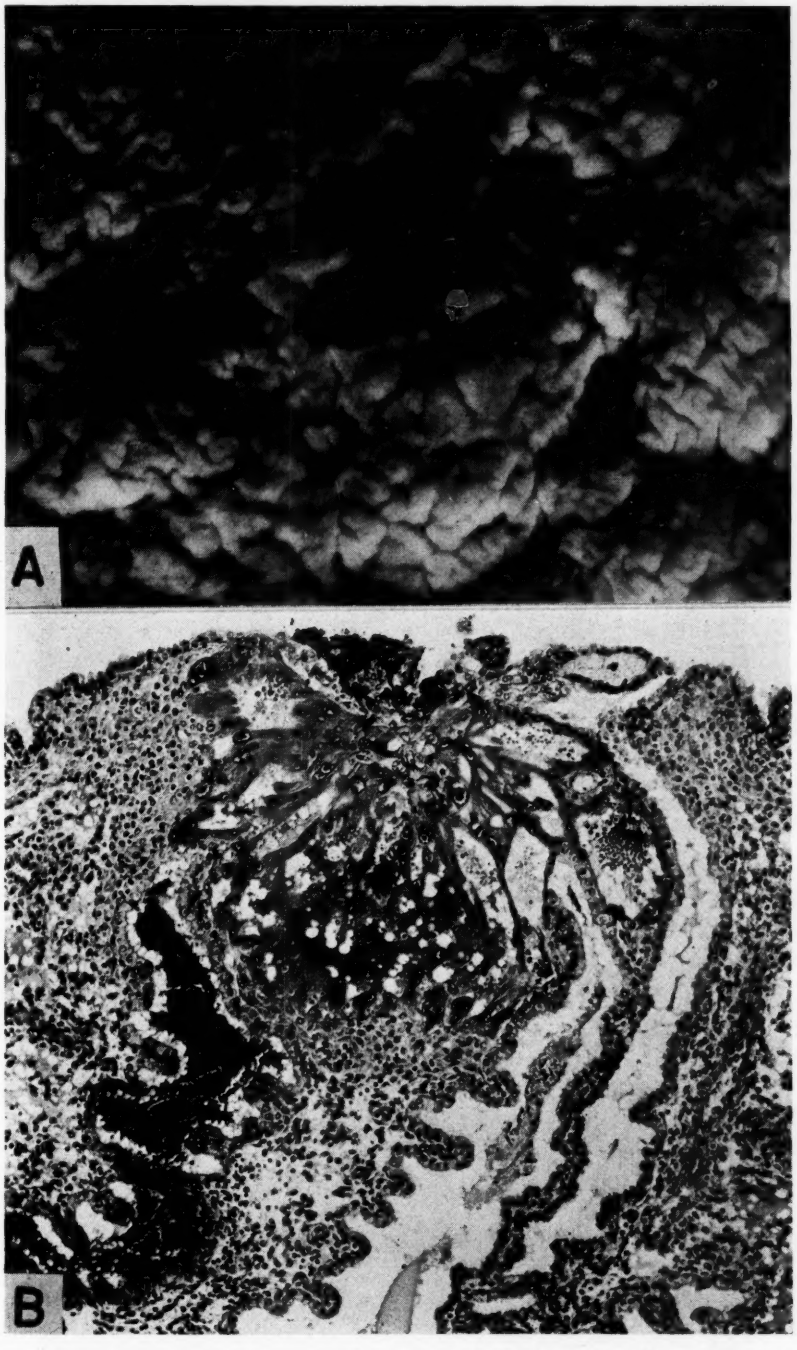

Fig. 5.—An abnormal human ovum, about 11 to 12 days, consisting of syncytiotrophoblast only. Carnegie No. 8329.

A, A gross view of the intact implantation site, photographed under fluid after fixation. Sequence 2 × 22.

B, A medium power photomicrograph of the greatest diameter to show the lack of embryo, chorionic cavity, or cytotrophoblast. Section 13-2-3 × 100.

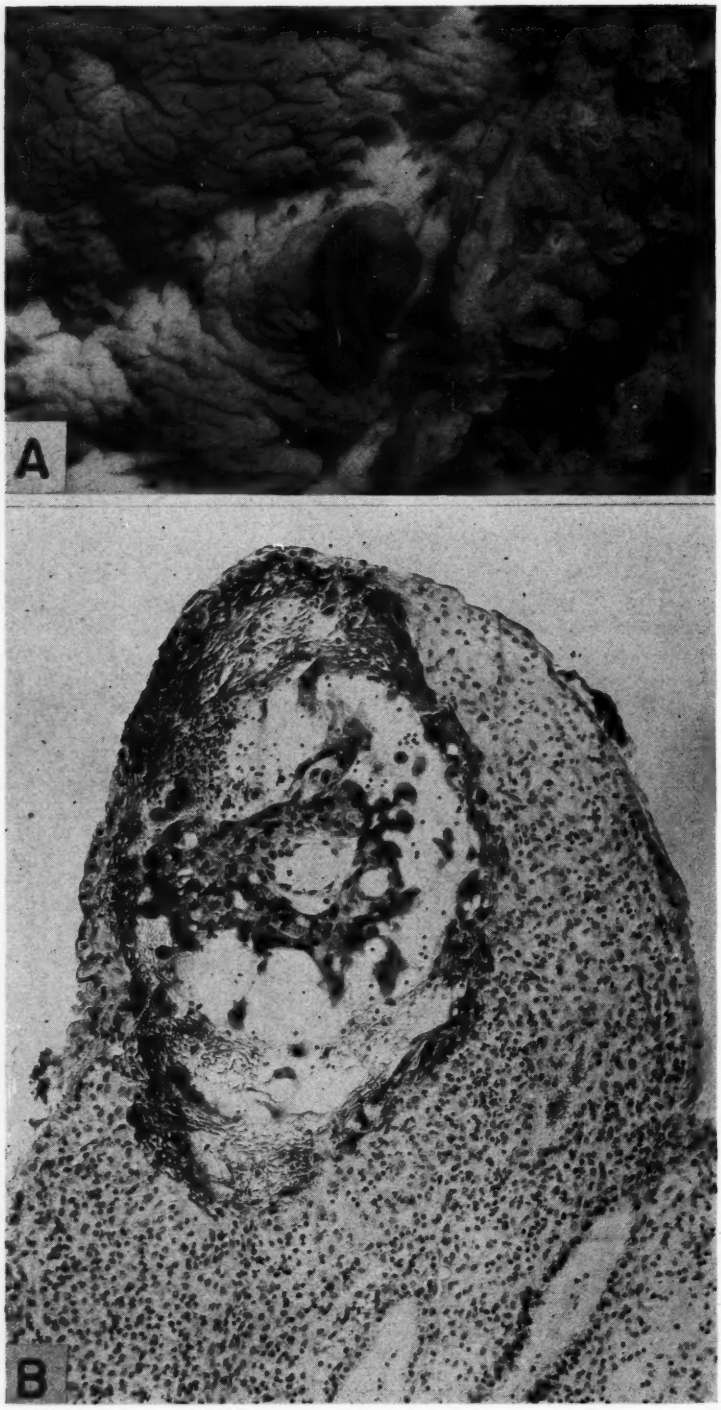

Fig. 6.—An abnormal human ovum, about 13 days, showing a polypoid type of implantation, a poor trophoblast, and no embryo. Carnegie No. 7771.

A, A gross view of the intact implantation site. Sequence 1 × 14.

B, A medium power photomicrograph of the section through the greatest diameter of the ovum. Section 3-4-1 × 100.

type of implantation near the lateral sulcus of the uterine cavity. Grossly, the remainder of the endometrium showed no polyps. Hence it seems unlikely that this ovum just happened to implant on the only polyp present. It is more probable that this type of implantation represents a deviation from the usual type seen in Figs. 2,A and B. Aside from lack of an embryo, the trophoblast itself is of poor quality so that this latter feature may account for a poorly embedded ovum. Regardless of the reason for this feature of the specimen the type of im-

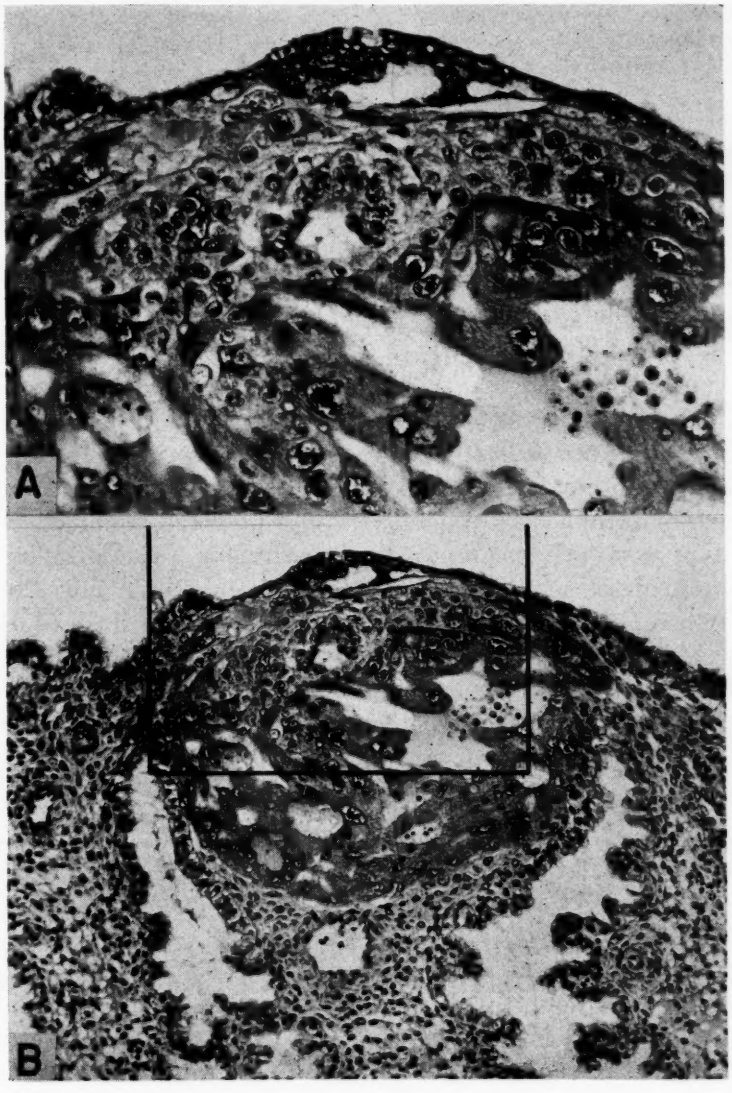

Fig. 7.—An abnormal human ovum of about 11 days without a chorionic cavity. Carnegie No. 8370.

A, A high-power photomicrograph of the embryonic disc and immediately surrounding trophoblast. Note the lack of primitive endoderm (compare with Fig. 2, A). This figure represents the portion of the picture blocked out in Fig. 7, B. Section 6-3-5 × 300.

B, A medium power photomicrograph of the section through the greatest diameter of the ovum and surrounding endometrium. Note the horizontal laminated arrangement of trophoblast (compare with Fig. 2, A). Section 6-3-5 × 150.

plantation cannot possibly explain the lack of an embryo within the ovum. It will be recalled that the previous specimen consisting of trophoblast only had a very adequate implantation whereas those shown in Figs. 10,A and B, possessing polypoid or shallow implantation have essentially normal embryos. Hence the poor quality of the present specimen is probably not due to extrinsic factors in the environment but rather to the intrinsic quality of the fertilized ovum itself. Certainly this 36-year-old patient shows no marked degree of clinical infertility with four previous normal children and only one spontaneous abortion.

4. *Ovum Without Chorionic Cavity.*—

This ovum (Fig. 7) is markedly abnormal in that the chorionic cavity is absent for all practical purposes. There is, however, a small amniotic cavity just beneath the curved embryonic disc (Fig. 7,A). The latter is also apparently defective in that no primitive endoderm is observed although the ectoderm is essentially normal. The lack of chorionic cavity accounts for the relatively small size of the specimen although the trophoblast is normal in amount for this stage of embryonic development, i.e., 10 to 11 days. The lack of endoderm and small size of the chorionic cavity—a lineal descendant of the segmentation cavity of the blastula—suggest some primary defect in the primitive trophoblastic shell of the blastocyst since the latter has to do with the formation of both of these structures (Heuser and Streeter[10]). Even though the primitive trophoblast seems to have been abnormal in these respects it was able to form syncytio- and cytotrophoblast in relatively abundant amounts. This tissue, while essentially normal in amount, is poorly arranged. There is a large amount of syncytiotrophoblast at the implantation, or embryonic pole, and a large amount of cytotrophoblast at the abembryonic pole. Thus, instead of these two tissues being concentrically arranged, the syncytio- surrounding the cytotrophoblast, they are more or less laminated. Hence, it would appear that although there is an abundance of trophoblast the primary defect lies within the primitive ancestor of this tissue. The embryo, paradoxically, while originally normal, will probably become increasingly abnormal because of a poor placenta and membranes.

The surrounding endometrium (Fig. 7,B) is normal and in the twenty-fourth day of the cycle. It shows only the usual slight progestational hyperplasia associated with all early pregnancies of this age.

It is difficult to evaluate this specimen in terms of the clinical outcome of the pregnancy. It is doubtful, however, whether the embryo would have developed into more than a nodular mass of cells within an amniotic cavity. Such specimens, classified in the Carnegie Collection[1] as Pathological Ova, Group IV, consisting of chorion, amnion, and nodular embryo, are one of the most common abortuses seen in clinical obstetrics. It appears impossible to blame the general maternal environment for this defective ovum in view of the normal endometrium and the fact that this 37-year-old patient has had four normal children and only one spontaneous abortion.

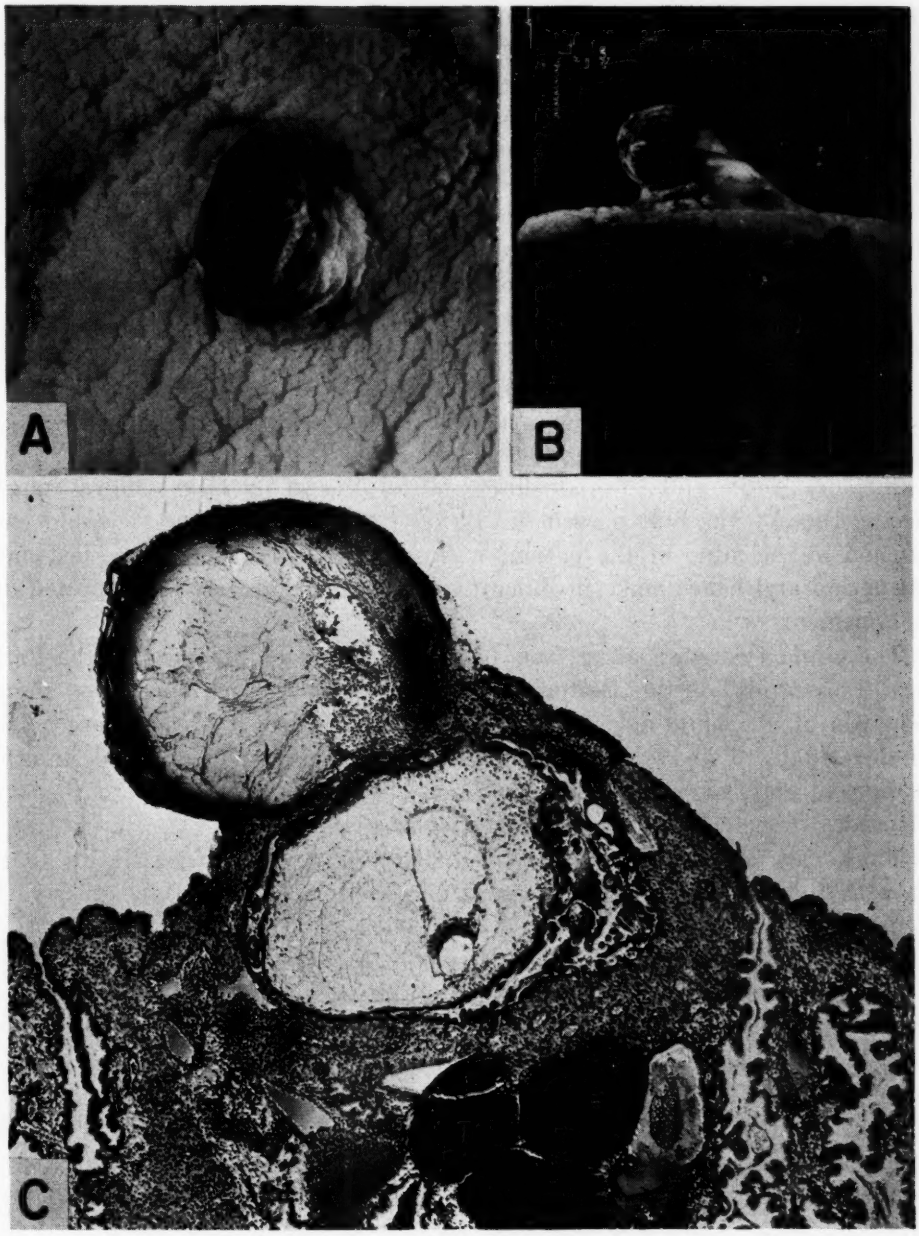

Fig. 8.—An abnormal human ovum of about 15 days showing defective or hypoplastic trophoblast. Carnegie No. 7800.

A, Surface view of implantation site to show hemorrhage. The wrinkled tissue is the surface of the surrounding endometrium. Sequence 2 × 8.

B, Lateral view of implantation site. Sequence 3 × 8.

C, Low-power photomicrograph of section through greatest diameter of the ovum and surrounding endometrium. Note extreme lack of adequate trophoblast. Simple villi should now be present (compare with Fig. 2, B). Section 15-1-3 × 35.

5. *Ovum With Hypoplastic Trophoblast.**—

On the basis of the clinical history and embryonic development, this specimen (Fig. 8) were it normal should be similar to the one shown in Fig. 2,B. However, the trophoblast is extremely defective (Fig. 8,C) and consists of only a small but variable amount of syncytiotrophoblast. At this stage of development the chorion should have well-developed, simply branching villi on the surface. The embryo is essentially normal and possesses a bilaminar germ disc, yolk-sac, and amnion.

The type of implantation is normal for this stage of development and shows maternal hemorrhage (Figs. 8,A and C) exuding from the defect in the overlying decidua capsularis. The endometrium is normal for this stage of pregnancy and shows early decidual reaction around the ovum as well as elsewhere. The massive hemorrhage within the gland beneath the ovum is normal and is analogous to that which exudes from the surface of the implantation site. Such hemorrhage, within the uterine cavity and endometrium adjacent to the ovum, was first described in the Macaque monkey by Hartman[15] on page 45 of his classic monograph and termed the "placental sign." It coincides roughly with the time of the first missed menstrual period. If profuse, it could cause confusion in the mind of the patient with respect to the time of the last menstrual period and hence make it difficult to estimate accurately the expected date of confinement.

The clinical counterpart of this pregnancy has been observed in the Pathological Laboratory of the Boston Lying-in Hospital. Such specimens show a hypoplasia of chorionic development with subsequent bald areas where no villi have developed. This results in insufficient placental tissue to nourish an otherwise normal embryo. The latter then dies, becomes macerated, and the ovum aborts toward the end of the first trimester of pregnancy.

Thus, this 35-year-old patient, who had been perfectly fertile up to this time with four normal pregnancies and no abortions, was destined to have her fifth pregnancy end in miscarriage.

6. *Ovum With Malposition of Embryonic Disc.*—

This otherwise normal 12-day ovum (Fig. 9) presents a curious anomaly in the position of its embryonic disc. Ordinarily such a specimen in this stage of development shows the embryo lying more or less parallel with the adjacent trophoblast (Fig. 2,A). This maloriented embryo (Fig. 9,C) probably occupied a normal position earlier because of its normal amniotic development. The amnion has been shown by one of us (A. T. H.) to delaminate in situ from adjacent trophoblast beginning in the 7-day ovum.[16] Hence it appears that this otherwise normal embryonic disc has recently shifted its position due to some unknown factor. Examination of serial sections other than the one here illustrated show that the edge of the germ disc is still attached to the trophoblast in a fashion similar to that shown in Fig. 10,A. It may be that growth of the amnion and chorionic connective tissue mechanically swung the germ disc into this bizarre position by virtue of the attached point acting as a fulcrum or hinge.

*Two other previllous specimens in this series, Carnegie Nos. 7770 and 7850 show minor degrees of trophoblastic hypoplasia. They are not described in this paper but have been described elsewhere in an earlier publication,[14]

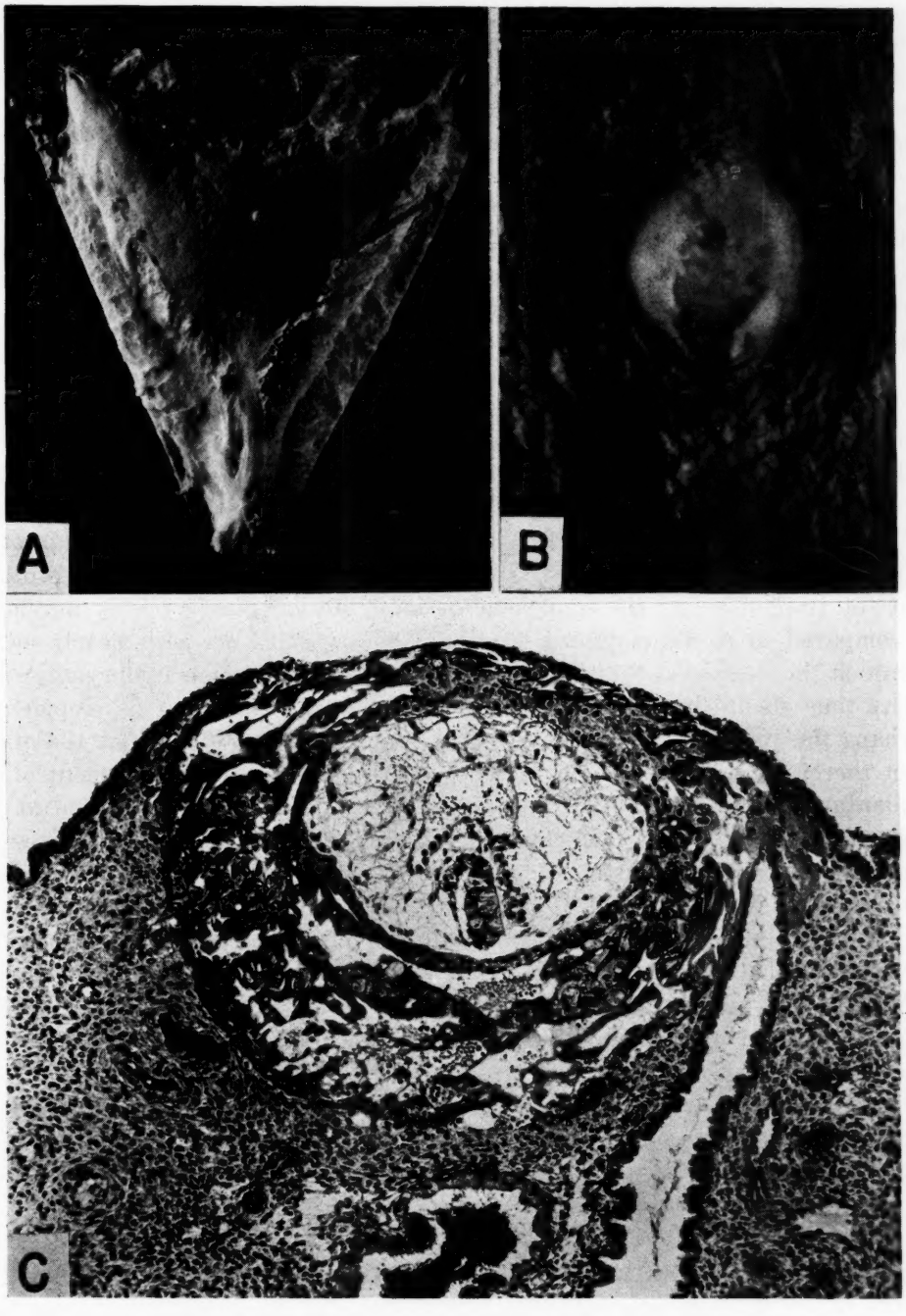

Fig. 9.—An essentially normal 11-day human ovum showing malorientation of the embryonic disc. Carnegie No. 8299.

A, A gross picture of the posterior wall of the uterus showing position and relative size of implanted ovum. Sequence 2 × 1½.

B, More highly magnified view of intact implantation site and surrounding normal endometrium. The defect in the endometrium overlying the ovum is normal. Sequence 4 × 22.

C, A medium power photomicrograph of the section through the greatest diameter of the ovum with adjacent normal endometrium. Note embryo turned on edge (compare with Fig. 2, A). All other parts of the ovum are normal for this stage of development. Section 11-6-5 × 100.

The implantation site, however, is particularly free from evidence of external damage (Fig. 9,A and B) so that operative trauma can probably be ruled out. Also, it should be pointed out that this specimen was removed in the same manner as all the other twenty-eight in our series and only one other (Fig. 10,A) showed anything approaching this curious embryonic anomaly.

Whether this patient would have ultimately aborted or not is impossible to say. It is quite possible that the germ disc would ultimately have freed itself from trophoblastic attachments and become reoriented again in the normal fashion. It is perhaps worthy of note that this 27-year-old patient had had three normal children and one spontaneous abortion previously. The cause of the latter was not determined from her clinical record.

7. *Ovum With Shallow Implantation and Other Anomalies.*—

This early villous ovum (Fig. 10,A), estimated to be about 13 days of age, shows severe deviations from the normal, none of which, either individually or collectively, may necessarily cause abortion. The most striking abnormality is its polypoid type of implantation. The curious buckling of the embryonic disc with a portion of the latter still attached to the trophoblast at the implantation pole of the ovum is nearly as striking. It is interesting and perhaps significant that the trophoblast at the embryonic or implantation pole is poorly developed as compared to its development elsewhere. Early villi are seen nearly everywhere on the surface of the chorion except at the implantation (embryonic) pole where they should be most highly developed. This anomaly of development is perhaps the primary one in the specimen with the probability that the others stem therefrom. Thus, the failure of proper trophoblastic development at the implantation pole may have resulted in the shallow or polypoid type of implantation. This in turn subjects the projecting ovum to mechanical pressure from the opposite wall of the uterus to which the normally implanted ovum is not exposed. At any rate, it appears that the distortion of the chorionic cavity and the buckling of the germ disc could be explained by mechanical pressure on the abnormally exposed ovum. The apparent similarity of the germ disc, in section, to that of a miniature sea horse is amusing. About the only thing one can be certain of with respect to the future of the embryo is that it won't become a sea horse.

Of interest in the clinical history of this 37-year-old patient is that she has given birth to ten normal children but has never had any spontaneous abortions! Whether this pregnancy would have been her first failure is anyone's guess.

8. *Shallow Implantation of Otherwise Normal Ovum.*—

The abnormality of this 12-day specimen (Fig. 10,B) is probably more apparent than real. To be sure it is somewhat more shallowly implanted than others of its general developmental age. However, the excessive hemorrhage from its normally defective decidua capsularis gives it a more polypoid appearance than its depth of implantation would actually warrant. No attempt is made in the illustration to give any microscopic details since the ovum itself is as morphologically normal as the one shown in Fig. 2,A. Certainly the endometrium is as normal as any in the entire series, being in the twenty-sixth day of the menstrual cycle with the usual progestational hyperplasia.

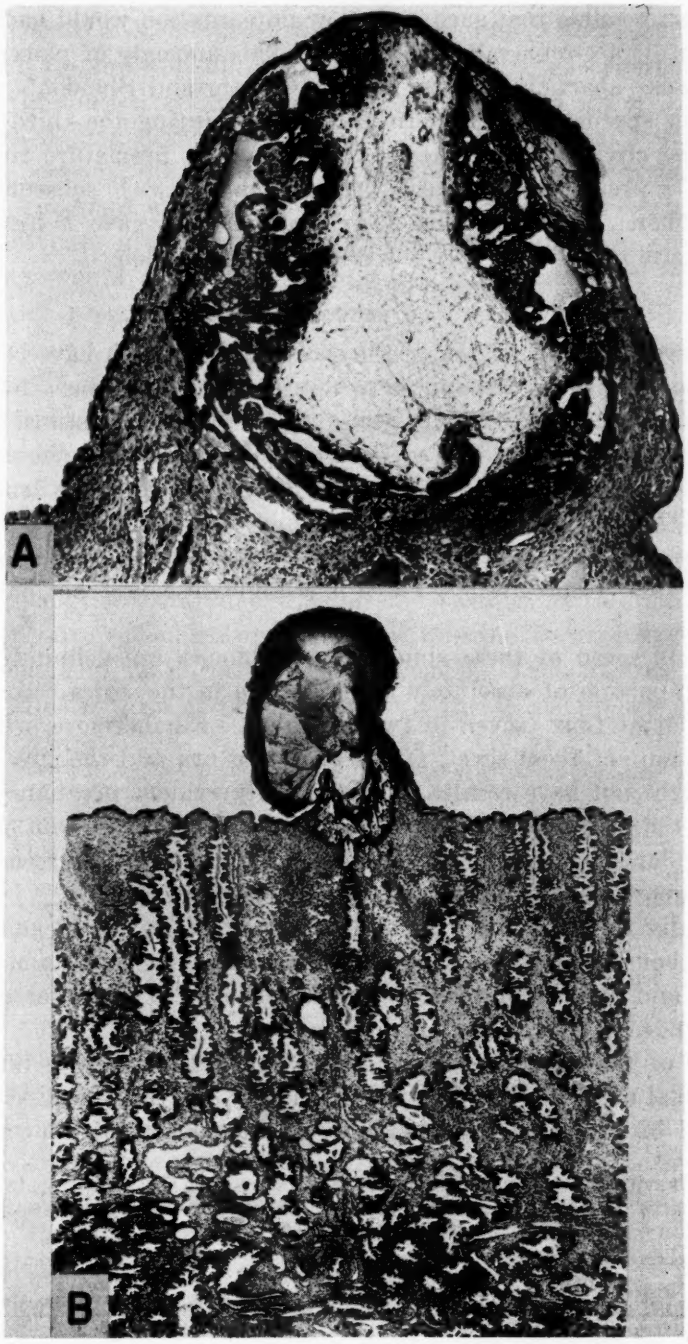

Fig. 10.—Two abnormal human ova showing various degrees of superficial implantation.

A, An abnormal 13-day specimen showing polypoid implantation, focal hypoplasia of trophoblast at implantation pole, distortion of chorionic cavity, and buckling of the germ disc. Carnegie No. 8290, section 25-2-4 × 60.

B, An otherwise normal 12-day specimen showing a somewhat shallow implantation with hemorrhage from the abembryonic pole. (Morphologic details of this stage of human development may be seen in Fig. 2, A.) Carnegie No. 8000, section 11-3-3 × 20.

It is doubtful whether this pregnancy would have resulted in abortion. It is, however, possible that such a shallow implantation would have resulted in the formation of a circumvallate placenta. This anomaly of placental development may cause abortion (4.5 per cent of Hertig and Sheldon's series[12]) but many of such specimens go to term. However, during the third trimester of pregnancy the circumvallate placenta may result in premature rupture of the membranes or premature separation of the margin with subsequent onset of premature labor. Clinically this 29-year-old patient gave a history of four normal full-term labors with only one spontaneous abortion.

Discussion

Of the twelve abnormal ova in the series, ten of which have been described in some detail while the remaining two with slight hypoplasia of the trophoblast were merely mentioned in passing, only seven were destined for probable or certain abortion. These showed defective blastomeres, trophoblast only, absent embryo, absent chorionic cavity, and markedly defective trophoblast, respectively. The remaining five showed minor degrees of trophoblastic hypoplasia, malorientation of the embryo, and various degrees of shallow implantation of the ovum, respectively. These five might or might not have aborted—probably not.

Since only seven of these abnormal pregnancies are definitely destined to abort, the proportion of absolutely defective ova in the series becomes approximately one out of four (seven in twenty-eight). Furthermore, when it is considered that four of these seven (the segmenting ova and the tiny mass of trophoblast) might not have resulted in a clinically evident pregnancy, it becomes evident that the proportion of three definite clinical abortuses out of twenty-five definitely implanted pregnancies (12.0 per cent) is in close agreement with the spontaneous abortion rate of approximately 10 per cent.

Admittedly this series is too small to permit of statistical analysis. However, it was thought advisable to compare such factors as age, number of normal pregnancies, and number of abortions in the histories of the other patients from whom either normal or no ova were obtained.

The age of the patients in each series is not significantly different; those yielding normal ova averaged 33.1 years of age, while those producing abnormal ova averaged 32.5 years. The remainder of these data are shown in Table I.

TABLE I. PREVIOUS NORMAL PREGNANCIES AND ABORTIONS, 136 POTENTIALLY PREGNANT PATIENTS IN WHOM 28 EARLY CONCEPTUSES WERE FOUND (16 NORMAL AND 12 ABNORMAL)

	NORMAL CONCEPTUSES	ABNORMAL CONCEPTUSES	CONCEPTUSES NOT FOUND	ENTIRE SERIES
No. cases	16	12	108	136
Average no. previous preg.	5.62	5.58	4.76	4.94
Average no. previous abort.	0.50	0.83	0.56	0.59
Percentage of previous abort.	9.09%	13.0%	10.6%	10.6%

It is evident that the sixteen patients from whom normal ova were recovered had had, on the average, almost one more previous normal pregnancy

than did the 108 patients whose uteri were nonpregnant. The patients who produced abnormal ova, however, did almost as well as the normally pregnant group with an insignificant difference of only 0.04 previous normal pregnancies in favor of the normal group. Moreover, the abnormal group had 0.82 more previous normal pregnancies than did the nonpregnant group. In the matter of previous abortions, the abnormally pregnant group had only 0.33 more than the normally pregnant group and only 0.27 more than the nonpregnant group. Whether these data are statistically significant or not we do not know. The data, however, would appear to indicate a slightly increased fertility in the group normally pregnant as compared to either the abnormally pregnant or nonpregnant group. It is interesting to note, furthermore, that in this entire group of extremely fertile women, one spontaneous abortion had occurred for every 8.4 normal pregnancies (10.6 per cent); the normally pregnant group aborting 9.09 per cent of their previous pregnancies while the abnormally pregnant group had prematurely lost 13 per cent of theirs. These figures, it will be remembered, are very close to the 10 per cent incidence of spontaneous abortion among the pregnant population at large.

In an attempt to determine whether the location of the implantation site of these twenty-five embedded pregnancies within the uterus played any part in the determination of its normality or abnormality, Table II was compiled. It will be recalled that three of the ova were still free in the uterine cavity.

TABLE II. POSITION OF OVA IN UTERUS AND THEIR RELATION TO THEIR CORPORA LUTEA OF ORIGIN

OVA	NO.	POSITION IN UTERUS		CORPORA LUTEA OF ORIGIN			
		ANTERIOR	POSTERIOR	SAME	OPPOSITE	FREE	UNKNOWN
Norm.	16	6	10	10	5	0	1
Abnorm.	12	6*	3*	5	3	3	1

*The free morulae account for three being on neither the anterior nor posterior wall of the uterus.

It is evident that the normal ova tend to be implanted on the posterior wall whereas the abnormal ones tend to be on the anterior wall although this correlation is by no means absolute. It is interesting that of the first 12 specimens found, this correlation was absolute.[3] Dr. William E. Studdiford, in commenting on this apparent fact, pointed out that the series was too small to allow any conclusions. It is still too small for generalization but the trend, as stated, is still apparent.

With respect to the side of the uterus on which the ovum implanted in relation to its corpus luteum of origin there appeared to be no correlation, as can be seen in Table II, for approximately one-third of each series embedded on the opposite side of the uterus. In no instance, however, were any ova, either good or bad, found below a line drawn halfway between the fundus and lower uterine segment. Therefore, at least none of these pregnancies were destined to be complicated by placenta previa.

Summary

Over a period of ten years, twenty-eight early conceptuses have been found in a group of 136 potentially pregnant women of known fertility who submitted to hysterectomy for a variety of therapeutic reasons. Twelve of these early human ova were abnormal and of these seven were certainly destined to abort. Four of the latter might not even have caused clinical evidence of pregnancy because of their extreme abnormality.

The ova destined to abort, either with or without evidence of their ability to produce clinical pregnancy, showed such fundamental defects as multinucleated blastomeres, absence of embryonic disc and/or chorionic cavity, or profound hypoplasia of the future placental tissue. None of these patients in whom abnormal ova were found showed any clinical or pathological evidence that maternal environment per se played any part in the production of the abnormal ovum. In other words, the endometrium was normal in all cases. The evidence, such as it is, indicates that the defective fertilized ovum is due to intrinsic "germ plasm" quality rather than to its environment and is the main factor in the production of spontaneous abortion.

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Discussion

DR. LYMAN W. MASON, Denver, Colo. (by invitation).—The theoretical considerations of this factual presentation are limitless. There are also clinical or practical considerations.

Dr. Mall, as Dr. Hertig has said, was of the opinion that defects in the maternal environment, or faulty implantation, were the cause for the pathological conceptuses which he found. These were usually concerned with evidences of infection and inflammation. His material, mostly spontaneous abortions, was contributed largely by clinicians throughout the country, sometimes with, but frequently without, the attached secundines or decidua. They

were of all ages, none so young, of course, as those which have been presented today. One cannot escape the belief that many, if not most, of these inflammatory changes were post-abortal, rather than the cause for the pathological conceptuses which were found.

The opposing viewpoint, viz., that the abnormal conceptuses are caused by defects inherent in themselves, has been presented today, on material which is much more significant. The case has been made increasingly strong for this viewpoint, especially by the work of Corner on the domestic sow, in which abnormal conceptuses are found side by side with normal ones in the same environment. Dr. Hertig has called attention today to the fact that in the cases shown, the endometrium was normal. One is impressed by the ten per cent mentioned by Dr. Hertig. This is the incidence which seems to run through all abortions, in human beings as well as that found by Corner in the sow. Must we accept this ten per cent of abortions as inevitable?

If one accepts pathology in the conceptus as due to faults inherent therein, and if we reject Mall's belief in maternal environmental defects as a cause, then it logically follows that attempts to save so-called "threatened abortions" are destined to failure, since they represent, not the beginning of trouble, but the end of a damaging process which is already past hope.

Also, it seems quite probable that cases of occasional menorrhagia and lengthened menstrual intervals in women whose menstrual cycles are usually normal, usually followed by a period marked by increased discomfort and increased flow, may well represent abortions of conceptuses such as have been described by Dr. Hertig.

Whether the fault is intrinsic in the conceptus, or is secondary to defective maternal environment, little has been accomplished in determining the fundamental cause of the pathological changes observed in the conceptus.

In the study of sterility, with which the presentation of Dr. Rock and Dr. Hertig is directly concerned, some progress has been made in semen specimens as a whole, based upon Dr. W. W. Williams' original work with bulls, but little as yet upon the individual sperm, which appear normal morphologically, although here we have millions to compare with each other in the same specimen. The problem is much more difficult for the relatively rare egg, fertilized or otherwise, which is recovered.

Considerable has been accomplished in studies along embryonic and genetic lines in some of the plants, and in some of the lower animal forms, especially in the Drosophila and Paramecium. It has been found that there are genelike bodies, apart from those in the chromosomes, in the cytoplasm, which may undergo mutations, and thereby profoundly alter the reactions of the cells to other tissue cells and to each other. These characteristics are transmissible through the cytoplasm of the cells, and not the chromosomes. Some of these mutations can be made to occur, and controlled to some extent. Such has been shown to account for a susceptibility to carbon dioxide in some Drosophila, for a certain type of male sterility in corn, and for defects in the plastids of some of the green plants which cause them to lack chlorophyll. It may be that environmental factors, physical or chemical, as yet unrecognized, are the cause of such mutations, temporary so far as the individual is concerned, involving only certain ova or spermatazoa, giving rise to products of fertilization which are abnormal. It may be possible, therefore, that environmental factors may not entirely be ruled out by the microscope, but may lie beyond what can be seen. One can not see in the microscope, for example, the causes for an allergy which must represent altered cells in tissues, which may suddenly appear in an individual never before affected.

In a long interest in sterility, with which the subject of abortion forms an integral part, from my own observations, from all I have read, and from all I have heard, I do not think that either of these fundamental concepts of spontaneous abortion has been proved to the entire exclusion of the other. In Hertig's and Rock's cases, there were maternal factors, which admittedly justified hysterectomies, in spite of normal-appearing endometrium, and hysterectomies are not done by outstanding gynecologists for minor indications. It must also be remembered that by the time the conceptus reaches the uterus, it is not a sperm or an ovum but a morula, composed of many cells, which has been subjected to environmental factors from the time of fertilization and before.

I am sure that it is the general belief that the study of these extremely early conceptuses, which has been presented today by Drs. Rock and Hertig, has advanced us much along the road, at the end of which lie the answers to the "whys" and the "hows" asked by those who concern themselves with the problems of human reproduction.

DR. KARL WILSON, Rochester, N. Y.—I desire to refer to a case of a 12-day ovum. It was obtained accidentally in an endometrial biopsy and we have the whole ovum. It looks quite normal. It appears that this defect through which the ovum was implanted ought to be healed over now and whether that represents a potential abortion it is difficult to say. The high-power view of the embryo shows a very early yolk sac. (Fig. 1.) Fig. 2 shows the endometrium in which the ovum was implanted. My first impression was that there was too much edema here and I was wondering if that would indicate that this ovum would have perished anyway because of defective endometrium. If that were true it would indicate that abortion would occur. The patient menstruated normally two days after the biopsy was obtained. Whether she would have menstruated and cast off the ovum or whether the menstrual flow was due to loss of the corpus luteum one can hardly say.

DR. THADDEUS MONTGOMERY, Philadelphia, Pa.—This presentation has again raised the old question of the relative influence of heredity and environment in the production of congenital abnormalities and congenital disease.

The phenomena which are sometimes observed in binovular pregnancy would seem to have a possible bearing on the answer to this problem. For instance, one oftentimes finds within the content of the womb, in which the environment may be assumed to be uniform, a binovular pregnancy in which one fetus and placenta are quite normal and the other degenerated and dead. Occasionally there is also encountered a binovular pregnancy in which one pregnancy has undergone hydatidiform degeneration and the other is apparently a normal pregnancy.

However, in contradiction to this point of view, there are some cases reported in which apparently chorionepithelioma has followed a full-term pregnancy and apparently has arisen from retained bits of chorionic tissue and syncytium rather than from the elements of a new pregnancy. It is quite possible, therefore, that both heredity and environment play an important role in these early disturbances of placentation and embryonic development.

DR. D. PLASS, Iowa City, Ia.—I would like to raise the question as to whether the evidence presented proves that this is a genetic responsibility. The mere fact that the endometrium appears normal is not proof that the cells are functioning normally. I doubt very seriously whether this evidence would prove acceptable to a biologist for that reason. We are learning more and more that one cannot link morphology and function with any accuracy.

DR. ROCK (Closing).—Dr. Hertig will perhaps in closing tell us the average age of patients we worked with because it may be that in these women a larger proportion of eggs were already a little older than are those still fertile ova of postadolescent women in general. It has been shown in the guinea pig and rabbit that with increase of ovulation age of eggs the incidence of abortion increases. I would suppose that in like manner eggs, older because of the age of the woman herself, are probably more likely to abort. Certainly the incidence of abortion increases after the age of thirty-five years. It has been shown also in some of the experimental animals that fertilization with older spermatazoa—that is, sperm out of the testicle longer than in normal ejaculates—is very likely to accomplish abnormal fertilization or fail to activate the egg at all. Thus we may have defects arising from within the zygote itself.

Some very interesting work has been done by Chang in Pincus' laboratory in Shrewsbury on the effect on the conceptus of the time of its arrival in the uterus. If a fertilized rabbit egg, 2 days of age, is placed in the uterus of another normal rabbit the day before ovulation, it will fail to establish pregnancy. Chang did this work, using dozens of eggs, and concluded from percentage results that if a 2-day fertilized rabbit egg is placed in a rabbit just at

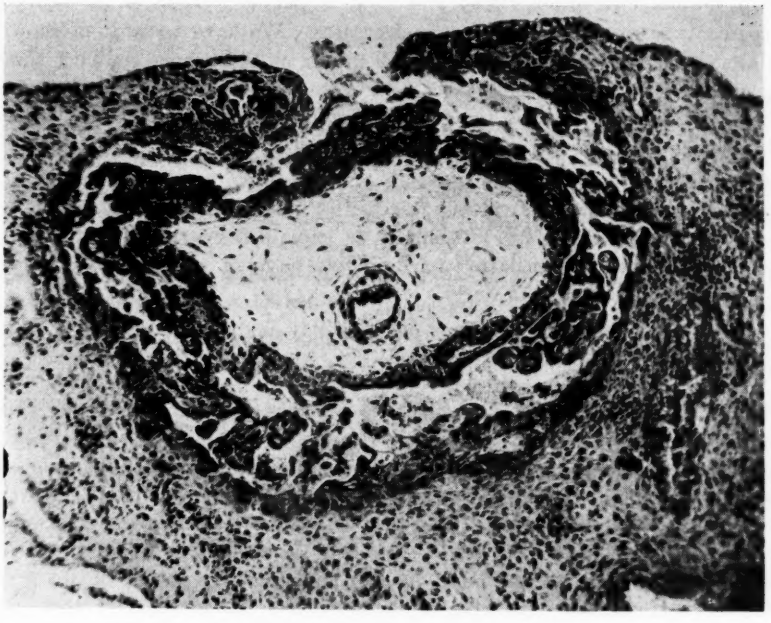

Fig. 1.—Early ovum of about 11 days.

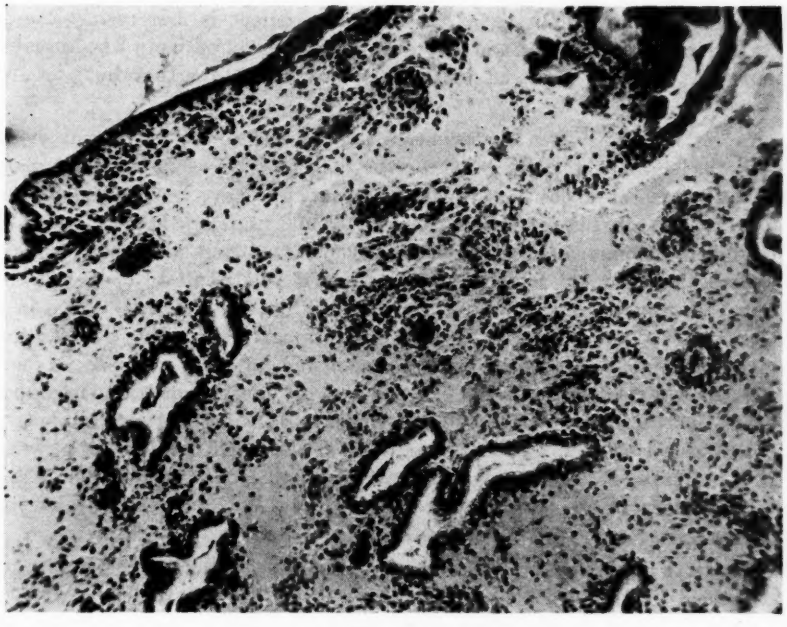

Fig. 2.—Edematous decidua.

ovulation there will be a somewhat smaller number of abortions but it is still almost 100 per cent. If, however, the 2-day fertilized egg is put in a two-day postovulatory rabbit then the percentage of normal conception rises; and if it is put in a four to six-day postovulatory rabbit the percentage of pregnancies again decreases. We have no way of knowing whether or not our abnormal conceptuses arrived in the uterus at the proper time. I think it is possible that sometimes we may attribute to the zygote the defect that we should attribute to tubal function or tubal fluid for, as Dr. Plass has stated, we know practically nothing of what the conceptus demands of the endometrium.

Dr Montgomery brought up the question of how do we get in binovular twins one bad and one good one. How can we attribute this to the fault of environment when here we have two eggs in the same environment? It might be explained on the time of arrival of those eggs in the uterus because a variation of only two days of either arrival or implantation might make all the difference in the world.

DR. JOSEPH BAER, Chicago, Ill.—I would like the essayist in his closing remarks to tell us something about the occurrence of genes in the cytoplasm.

DR. HERTIG (Closing).—Dr. Mason has raised the point as to whether this inflammatory-like infiltration of the leucocytes had some etiologic relationship to abortion. Dr. Mall, while a very eminent embryologist, apparently did not realize that all spontaneous abortions have as part of their final morphologic picture thrombosis, necrosis, and hemorrhage in the decidua. The leucocytic response to sterile necrosis is what he interpreted as inflammation. This is seen whether the corpus luteum is surgically removed or whether there is a blighted ovum or low-implanted ovum as the basis for the abortion. As to Dr. Mason's second point that threatened abortions are inevitable, I do not agree. About half of them do not abort irrespective of what is done. There is, however, a group of threatened abortions which without proper treatment will abort but can theoretically be salvaged by treatment. This is the relatively small group amounting to about 30 per cent of all abortuses or 15 per cent of threatened abortions. These potentially salvageable threatened abortions have normal embryos and chorions that are living at the time the patient is first seen. The presence of this group in a series of abortuses and hence in any series of patients who threaten to abort is the explanation for the increased salvage of threatened abortion by administration of estrogens.

With respect to Dr. Wilson's specimen, it is unique to get a normal ovum properly sectioned with the significant parts of the embryo in it from chance biopsy material. We have one such specimen at about 8 days which appeared to have been completely removed by biopsy, also, as in this case, in a sterility patient. That brings up the question of when is the best time to do an endometrial biopsy in sterility patients, and we feel it should be at the onset of menstruation or prior to implantation when it is difficult to damage a free-floating blastula. The yolk sac which Dr. Wilson mentioned is a beautiful early stage in the formation of this structure. Since nothing is known in its early formative period, this specimen promises to be unique. We had hoped for years to find an early yolk sac in the process of examining the uteri from these patients. The edema of the endometrium is probably within normal limits. Nobody can answer whether withdrawal of the chorionic support caused the patient to have her period within two days or whether she would have had it anyway. I think the ovum is a normal one. Dr. Wilson also asked whether the implantation site at the top should not have closed; in the normal 11- to 13-day ovum it is not really healed but is closed over by what Graf von Spee called "Schlusscoagulum."

With respect to Dr. Schwarz' question, the implantation pole of the ovum is almost invariably determined by the position of the embryo itself. In the rare case when that is not so and the ovum implants upside down, then one has a membranous insertion of the cord. What determines why the ovum should stick itself in the position it does is not known except that it implants with the embryonic pole toward the endometrium. The ovum itself may be sticky or there may be present some difference of electrical potential which attracts the embryonic pole to the endometrium.

I do not know much about the problem of binovular twins. We do know that we see normal twins along with abnormal ones. I have always felt that these mummified twins did not have as good blood supply as the others; their placentas are normally formed but often infarcted.

As to the point made about hydatidiform mole subsequent to normal pregnancy, I consider that to be a new pregnancy which has undergone hydatid degeneration. I feel that the chorionepitheliomas which follow normal pregnancy are the result of retained trophoblast which has undergone malignancy, but why that happens I do not know.

Dr. Plass's question whether these things are genetic has been answered by Dr. Rock: we do not know. It was our purpose to point out that here was a group of normal patients, 10 per cent of whose implanted ova were abnormal in the presence of an apparently normal environment.

The average age of these patients was 32.5 years in the group producing abnormal ova, and 33.1 years in those producing normal ova.

I think Dr. Rock's point about the time of arrival of eggs in the uterus is well taken and that may account for Dr. Mall's classic observation on the abnormality of the majority of ova in ectopic pregnancy because they certainly implant in an environment which is not normal and at a time when they should not be implanted in that location.

In answer to Dr. Baer, I know nothing about the genes within the nucleus. I can only say that these embryologic observations are in the "horse and buggy" phase of morphology; they have not been studied histochemically. We were content to find the ova and get serial sections made of them.

THE INFLUENCE OF DIETHYLSTILBESTROL ON THE PROGRESS AND OUTCOME OF PREGNANCY AS BASED ON A COMPARISON OF TREATED WITH UNTREATED PRIMIGRAVIDAS*

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THIS is a report of continued progress in the clinical evaluation of our concept concerning the action of diethylstilbestrol in human pregnancy. The basis for the use of diethylstilbestrol in pregnancy and the evidence for its progesterone-stimulating effect have been reviewed in a previous publication,[1] a clinical study in which the drug was shown to be beneficial in the treatment of threatened abortion and in the prevention of abortions that would have been anticipated because of previously lost early gestations. A preliminary report was also included on the use of stilbestrol for the prevention of late pregnancy complications in patients in whom pre-eclampsia, eclampsia, premature delivery, or stillbirth was anticipated because of their past medical or obstetrical histories. A larger series of such patients is being reported elsewhere.[2] Certain difficulties are encountered, however, in the evaluation of results in patients of this sort. In evaluating the results of stilbestrol therapy for threatened and chronic abortion, we had reliable figures on the spontaneous cure rates of these conditions as a basis for the analysis of our data. No such generally accepted figures are available, so far as we know, as a basis for evaluating any prophylactic therapy against complications of late pregnancy. It was for this reason that the present study was undertaken, the plan being to compare the late pregnancies of treated primigravidas with those of synchronous control primigravidas in order to determine whether the drug might have value in reducing the usual incidence of late pregnancy complications and fetal loss. Although the incidence of toxemia, premature delivery, and stillbirth in primigravidas has been extensively worked up in most obstetrical clinics, there is always the possibility that differences in prenatal care, dietary conditions, seasonal variations, etc., might influence results. In order to eliminate all possible variables it was deemed important to have a synchronous control group from the same clinic rather than to depend upon the data from previous years or from other clinics.

We have shown[3] that late pregnancy toxemia, premature delivery, and death of the fetus in utero are preceded by a premature deficiency of estrogen

*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

and progesterone. We have also presented evidence that this hormonal deficiency, once established, may be part of a vicious cycle in which lack of hormonal support, vascular deficiency, and toxin formation augment one another and that any one of these factors, unless corrected, may eventually lead to all three.[3] The high incidence of late pregnancy complications in primigravidas as compared with multiparas has been ascribed rather generally to mechanical factors that might cause a relative deficiency in blood supply to the uterus. Our studies have indicated[3] that any situation which affects adversely the blood supply to the uterus will interfere with the normal production and metabolism of the placental steroid hormones, estrogen and progesterone. The combined action of estrogen and progesterone, on the other hand, is characteristically one of increased myometrial and vascular growth. By the administration of stilbestrol and provision thereby of an extra stimulus for the production of estrogen and progesterone, we would not expect completely to avert all late pregnancy complications in all primigravidas but, if our concept is correct, the onset of such complications should be postponed, their severity reduced, and, in a certain proportion of patients who would ordinarily have no trouble until late in pregnancy, entirely prevented.

The Clinical Experiment

This study was carried out at the Boston Lying-in Hospital.* It was begun in April, 1947, and ended Jan. 1, 1949. A record was kept of all primigravidas who made their first visit before the twentieth week of gestation and whose condition was diagnosed as normal. No patients with known essential hypertension, diabetes, or nephritis were included. So far as was possible under the circumstances, alternate patients were interviewed and given stilbestrol.† A calendar dosage schedule was made out for each patient and written instructions were provided. The patient checked the calendar each day after taking her pills and was interviewed at each visit to be sure she understood the instructions and was faithful about taking the medication as prescribed. At the end of therapy, after thirty-six weeks, all left-over pills were returned and counted in order to obtain a further check as to whether or not instructions had been followed.‡ In all other respects there was no difference in prenatal care between the treated and control patients, nor was there any significant difference in their ages. Ninety-two to 93 per cent of both groups were under 30 years of age when first seen. The administration of stilbestrol was started between the twelfth and sixteenth weeks in 75 per cent of the treated cases and by the twentieth week in the remainder.

The drug was taken orally. In the dosage schedule originally recommended by us[1] (and still felt to be the closest to physiological) the amount taken is increased by 5.0 mg. at weekly intervals after the fourteenth week. This involves the use of 5.0 mg. tablets to supplement the 25.0 mg. pills in order to

*The authors are indebted to the medical and nursing staffs of the Boston Lying-in Hospital for their cooperation in making this study possible. Indispensable assistance and advice were given by Drs. Duncan E. Reid, William J. Mulligan, Arthur W. Tucker, Jr., and Samuel B. Kirkwood in the matter of abstracting records and checking on the diagnoses. We are indebted to Drs. Clement A. Smith and Stewart H. Clifford for advice in organizing the data on premature infants. The secretarial work involved and the all-important task of interviewing the patients, dispensing stilbestrol, getting back surplus pills, etc., etc., were performed by Mrs. Grace M. Harris, to whose perseverance and tact may be attributed the unusual cooperation of the patients in following instructions. She was assisted by Ethel Stewart, R.N., to whom we are also indebted for abstracting records. Tabulation of the data from the record abstracts as fast as they were received was performed by Mrs. Muriel G. Mann, thereby considerably simplifying the final task of the authors.

†E. R. Squibb & Sons supplied the 25.0 mg. tablets of stilbestrol used in this study.

‡A total of 415 primigravidas were started on stilbestrol. Twenty-eight of these had to be omitted from the study because of known gross errors in stilbestrol medication.

get the right dosage. In handling a large number of clinic patients it was felt that the use of two sorts of pills might lead to bad errors in dosage. The schedule was therefore modified. One-half of a 25.0 mg. tablet (12.5 mg.) was taken daily during weeks 12 and 13 and a whole tablet (25.0 mg.) daily during weeks 14, 15, and 16. At the start of the seventeenth week the dosage was increased to 50.0 mg. and maintained at this level through the twentieth week. It was then raised to 75.0 mg. for weeks 21 through 25, 100.0 mg. for weeks 26 through 30, and 125.0 mg. for weeks 31 through 35, when it was discontinued. When treatment was started after the twelfth week the initial dosage was always the one for the particular week of pregnancy when therapy was begun. This is dosage schedule No. 1, which was followed in the treatment of the first 152 primigravidas who, with 283 synchronous control primigravidas, comprise Series A (v.i.).

The schedule just described was employed in a number of abnormal patients in another study,[2] whose urinary pregnanediol was being followed by the method of Venning. In many of these cases the curves flattened out or even dropped towards the end of a five-week interval at one dosage level, instead of showing the normal gradual rise found in other patients taking gradually increased doses of stilbestrol. Therefore, the schedule was changed so that one and one-half of the 25.0 mg. tablets, 37.5 mg., were ingested daily during weeks 16, 17, and 18; two tablets, 50.0 mg., during weeks 19, 20, and 21; two and one-half, 62.5 mg., during weeks 22, 23, and 24; 75.0 mg. during weeks 25 and 26; 87.5 mg. during weeks 27 and 28; 100.0 mg. during weeks 29 and 30, 112.5 mg. weeks 31 and 32, 125.0 mg. weeks 33 and 34, and 137.5 mg. during the thirty-fifth week. In this manner (schedule No. 2), 235 primigravidas were treated. They and 272 synchronous control primigravidas comprise Series B (v.i.).

With the exception of an occasional complaint of nausea or itching of the skin, no toxic effect could be attributed to the stilbestrol as administered. In no instance was the drug discontinued or the dosage changed because of symptoms, despite which fact the symptoms disappeared. There were no deaths among the treated or control mothers of this study.

Comparisons Between Treated and Control Primigravidas

An over-all comparison of the incidence of late pregnancy complications is graphically presented in Fig. 1. According to statistical analysis,* the better total results among the treated patients in each category are significant, highly so as regards the incidence of toxemia and fetal mortality.

1. *Toxemia of Pregnancy.*—

TABLE I. INCIDENCE OF LATE PREGNANCY TOXEMIA

	SERIES A		SERIES B	
	TREATED	CONTROL	TREATED	CONTROL
Total no. of cases	152	283	235	272
Pre-eclampsia Grade I	5	18	3	12
Pre-eclampsia Grade II	0	2	1	5
Eclampsia	0	0	0	1
Totals	5 (3.3%)	20 (7.0%)	4 (*1.7%*)	18 (*6.6%*)
Totals A + B	Treated:	9 (*2.3%*)	Control:	38 (*6.8%*)

In Table I the incidence and type of toxemia are summarized. Throughout the rest of this paper, italics indicate statistical significance of the difference

*We are indebted to Jane Worcester, Dr.P.H., Assistant Professor of Biostatistics at the Harvard School of Public Health, for advice in the statistical analysis of our data and for a review of the final manuscript to check its statistical accuracy.

between control and treated cases. These figures show not only less toxemia on stilbestrol but also a reduction in the incidence of pre-eclampsia Grade II* and eclampsia, from *1.6 per cent* in the 555 controls to *0.26 per cent* in the 387 treated patients. In other words, what toxemia did occur was less severe.

In Fig. 2 the nine cases of toxemia among the treated patients are compared with the 38 cases among the controls. From a statistical point of view in such a comparison, it is unfortunate that we have only nine cases of toxemia among the treated patients. Despite the fact that such a small number of cases is not subject to statistical analysis, the data in Fig. 2 suggest that even pre-eclampsia Grade I in these nine women was less severe and later in its onset than it might have been if stilbestrol had not been taken. There were only two in whom the disease had its onset prior to the thirty-fourth week, as against over half of the 38 cases of toxemia in the control group. Toxic signs were also less severe in these nine patients. In none of them was the interruption of pregnancy indicated prior to two weeks before term; whereas in three control cases cesarean section had to be resorted to at 32 and 36 weeks, and in four others labor was artifically induced at 32, 35, 36, and 37 weeks, respectively, because of the increasing severity of toxemia (the case of interruption at the thirty-second week being in an eclamptic).

There were two fetal deaths in the nine toxic pregnancies that occurred despite stilbestrol treatment, as against five fetal deaths in thirty-eight patients with toxemia in the control series. Both of the fetal deaths in the stilbestrol-treated patients were associated with extenuating circumstances. One of the two women presented her first toxic signs (hypertension and albuminuria) at 21 weeks, after she had been on stilbestrol for only five weeks. Although she was clinically normal at her only previous visit at 16 weeks, when stilbestrol was started, it seems probable, considering the very early appearance of toxic signs and their persistence after delivery, that this patient had antecedent renal disease and should not have been classified as a normal primigravida. Even if this was a case of true toxemia, stilbestrol administration was not prophylactic, since, according to our experience in studying such cases,[3] the hormonal deficiency of toxemia is underway some four to eight weeks before the disease is clinically detectable. We have shown[4] that stilbestrol administration alone is of no value for the definitive treatment of established pre-eclampsia. This patient is also the only one of the 387 treated primigravidas who developed signs and symptoms diagnosed as Grade II pre-eclampsia. At 30 weeks she went into labor spontaneously and delivered a macerated, stillborn infant.

The other fetal death among the nine cases of toxemia on stilbestrol was in a patient who had pyelitis starting at 26 weeks and who discovered that the drinking of much tea preliminary to her prenatal visits was a means of obviating hospitalization. Her diluted urine contained less protein according to the qualitative test used in the clinic. Her ingenuity in this respect, together with her uncooperative attitude, made us suspect that she may not have taken her stilbestrol, despite the accuracy with which she marked her medication sheet and the fact that she returned the right number of pills when her pregnancy was completed. In addition to pyelitis she developed hypertension consistent with a diagnosis of pre-eclampsia Grade I, and at 32 weeks she delivered spontaneously a 3 pound infant which lived only three days.

2. *Spontaneous Premature Delivery.*—

According to the accepted definition of prematurity[5]—any child born alive weighing 2,500 grams (5½ pounds) or less—the total incidence of this abnormality was *2.8 per cent* in the treated cases as against *6.1 per cent* in the controls (Fig. 1).

*Throughout this paper the term "pre-eclampsia Grade II" refers to severe pre-eclampsia or preconvulsive toxemia, whereas "pre-eclampsia Grade I" refers to mild pre-eclampsia.

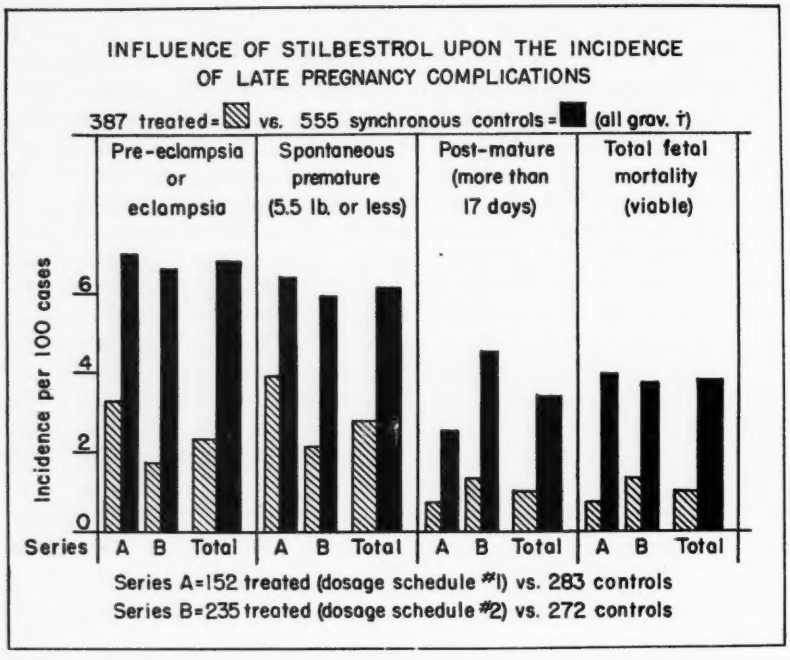

INFLUENCE OF STILBESTROL UPON THE INCIDENCE
OF LATE PREGNANCY COMPLICATIONS
387 treated = vs. 555 synchronous controls = (all grav. †)
Pre-eclampsia or eclampsia
Spontaneous premature (5.5 lb. or less)
Post-mature (more than 17 days)
Total fetal mortality (viable)
Incidence per 100 cases
0
2
4
6
Series
A B Total
A B Total
A B Total
A B Total
Series A=152 treated (dosage schedule #1) vs. 283 controls
Series B=235 treated (dosage schedule #2) vs. 272 controls

Fig. 1.

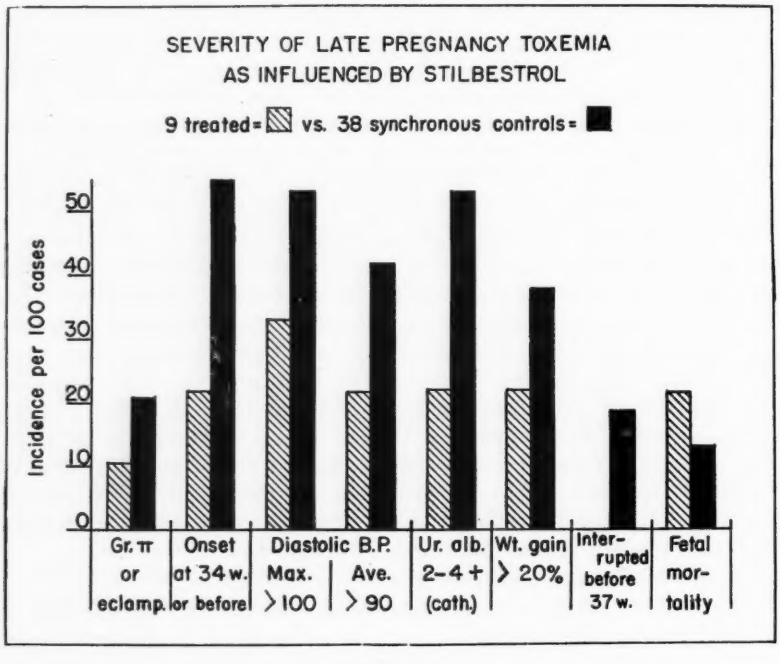

SEVERITY OF LATE PREGNANCY TOXEMIA
AS INFLUENCED BY STILBESTROL
9 treated = vs. 38 synchronous controls =
Incidence per 100 cases
0
10
20
30
40
50
Gr. π or eclamp.
Onset at 34 w. or before
Diastolic B.P. Max. > 100
Diastolic B.P. Ave. > 90
Ur. alb. 2-4 + (cath.)
Wt. gain > 20%
Inter-rupted before 37 w.
Fetal mor-tality

Fig. 2.

An important observation in this group of patients is the fact that if prematurity is defined on the basis of the expected date of confinement rather than of birth weight there is no difference between the treated and control groups. Among the 387 treated patients there were 42 (including one who had twins), or 10.8 per cent, whose only complication was spontaneous delivery more than two weeks before term. In the control group of 555 cases there were 66 such patients (including three who had twins), or an incidence of 11.8 per cent. In our first study,[1] stilbestrol administration was associated with a 33 to 47 per cent reduction of premature delivery in those who had previously delivered early. It was pointed out, however, that over 50 per cent of the women who had previously delivered early, regardless of how many times this had happened, did not carry to term on stilbestrol, although the fetal loss from prematurity was greatly reduced. It was inferred that in over half of these women factors other than hormonal were primarily responsible for this late pregnancy complication, the hormonal deficiency being a part of the end result and therefore a final contributory factor only. The findings in the present study suggest that factors other than hormonal account for most of the premature deliveries in primigravidas.

Despite the failure to reduce spontaneous premature delivery in primigravidas, as defined in terms of gestational age, medication with stilbestrol proved of real benefit to the infants of these women. There were nine deaths among the 69 infants of the control group whose only complication was spontaneous delivery more than two weeks before term, a mortality rate of *13 per cent. None* of the 43 babies of the treated patients who delivered early died.

In order to determine the cause for this strikingly beneficial influence of stilbestrol upon fetal salvage, the data on babies who were of comparable gestational age in the two groups were analyzed. In this analysis all twins were omitted, since there were more twins in the control than in the treated groups. (This excluded one of the fetal deaths in the controls.) In Series A there were five of the controls who gave birth between the twenty-fifth and thirty-second weeks. Since none of the treated women in Series A delivered during this interval, these five controls (and their four fetal deaths) are also omitted from the comparisons. The distribution of gestational ages in the remaining data analyzed is shown in Table II. The omission of infants that would weight the data unfairly against the prematurely delivered offspring of the controls resulted in a similar distribution of gestational ages in the two groups, and therefore a fair basis for the comparison of babies delivered prematurely with and without stilbestrol therapy. These are the cases that were used in compiling the statistics for Tables III, IV, and V, and for Fig. 3.

TABLE II. DISTRIBUTION OF GESTATIONAL AGES IN DATA ANALYZED FOR FIG. 3 AND TABLES III, IV AND V

		TREATED		CONTROLS	
Total number of babies		41		58	
Week of delivery	26 to 28	1	2.4%	1	1.7%
	30 to 32	1	2.4%	2	3.5%
	32+ to 34	3	7.3%	4	6.9%
	34+ to 36	9	22.0%	13	22.3%
	36+ to 38	27	66.0%	38	65.6%

TABLE III. DISTRIBUTION OF BIRTH WEIGHTS IN PREMATURELY DELIVERED INFANTS (OF COMPARABLE GESTATIONAL AGES—OMITTING TWINS)

WEIGHT AT BIRTH	STILBESTROL		CONTROLS	
5 pounds, 8 ounces or less	10	*24%*	28	*48%*
5 pounds, 9 ounces to 6 pounds, 9 ounces	23	56%	23	40%
6 pounds, 10 ounces or more	8	20%	7	12%
Totals	41		58	

TABLE IV. DISTRIBUTION OF LENGTHS AT BIRTH IN PREMATURELY DELIVERED INFANTS (OF COMPARABLE GESTATIONAL AGES—OMITTING TWINS)

CROWN-HEEL LENGTH AT BIRTH	STILBESTROL		CONTROLS	
18 inches or less	7	17%	19	33%
18⅛ to 18⅞ inches	4	10%	12	20%
19 inches or more	30	*73%*	27	*47%*
Totals	41		58	

TABLE V. DISTRIBUTION OF INITIAL WEIGHT LOSSES IN PREMATURELY DELIVERED INFANTS (OF COMPARABLE GESTATIONAL AGES—OMITTING TWINS)

WEIGHT LOSS IN PER CENT OF BIRTH WEIGHT	STILBESTROL		CONTROLS	
7% or less	12	29%	11	19%
7.1 to 11.0%	25	61%	29	50%
More than 11.0%	4	*10%*	18	*31%*
	41		58	

As shown in these tables and graphically depicted in Fig. 3, stilbestrol-treated women not only lost none of their babies but also had fewer babies which were actually premature in the matter of weight (Table III) and length (Table IV). Moreover, more of their babies were able to suckle, and to leave the hospital with their mothers. That the greater weight of more of their babies might have been due to water retention from exposure to larger amounts of steroid hormones seems hardly tenable, since fewer of these offspring lost over 11.0 per cent of their birth weight during the early days of extrauterine life (Table V).

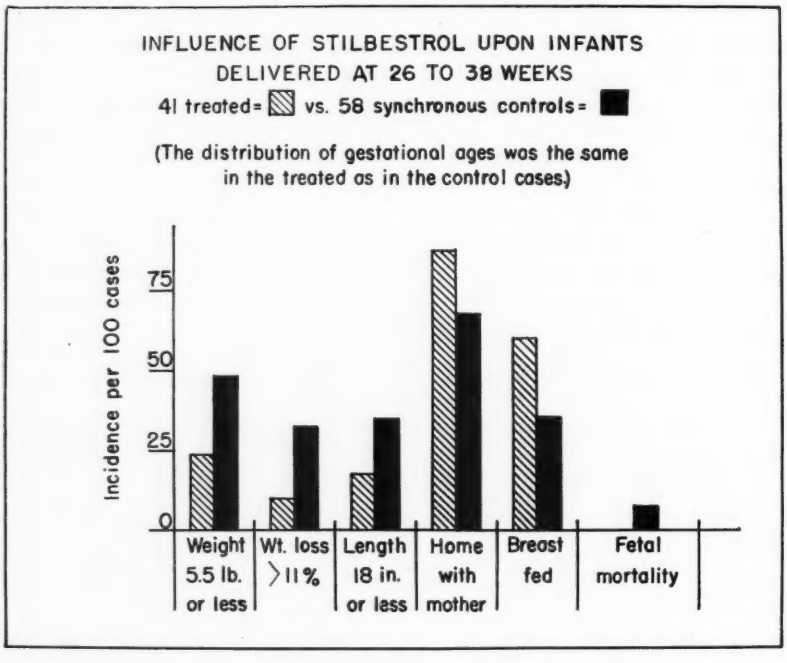


Fig. 3.

Scattergrams were made (Figs. 4 through 7) in order to see how the values for the weights and lengths of the premature infants of treated and control mothers fell in relation to curves based on averages. In these scattergrams

Figure 4

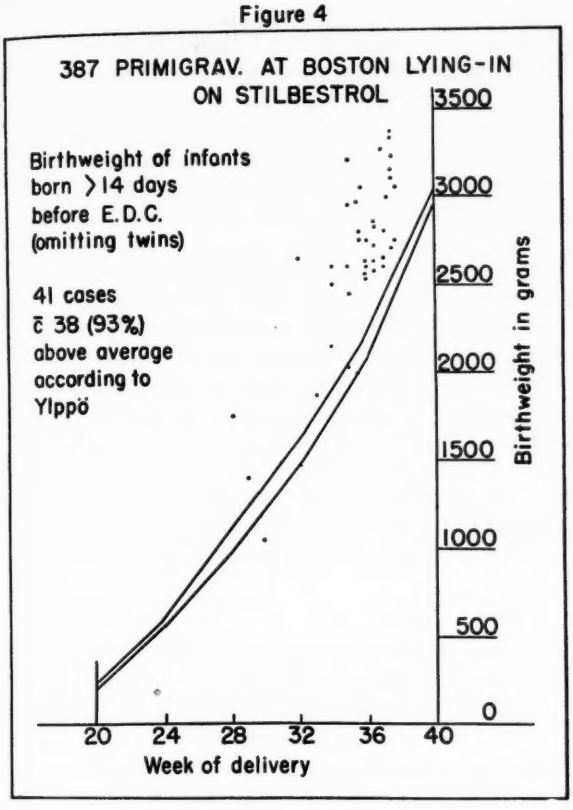


Figure 5

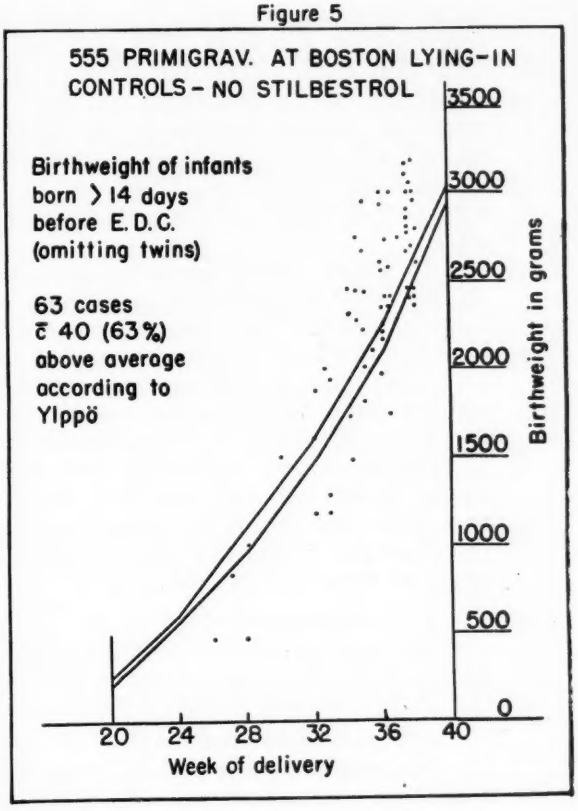


Figure 6

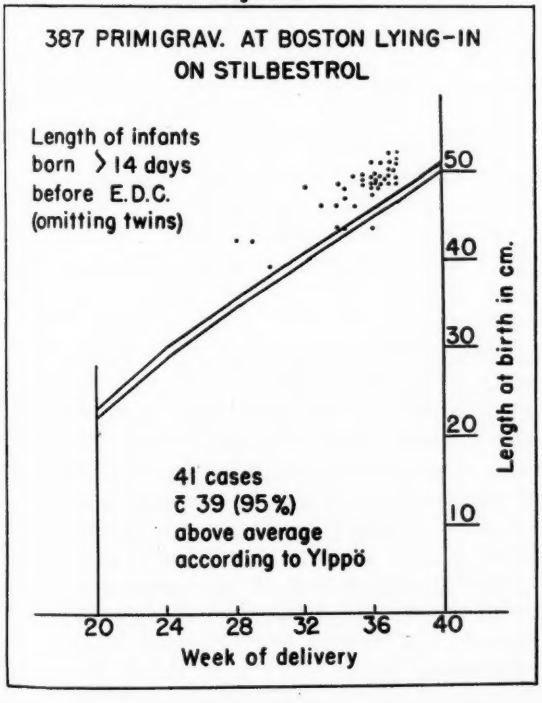
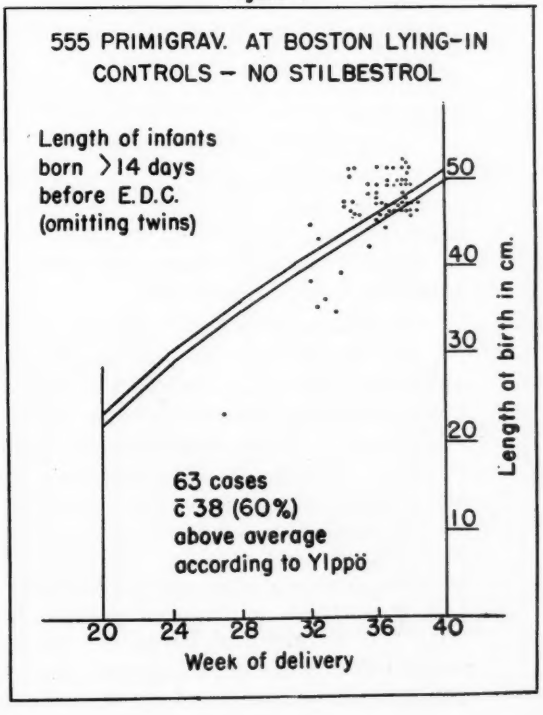


Figure 7



twins only are omitted. The upper curve in each of these four charts was determined by Ylppö in 1919 and the lower by Scammon and Calkins between 1922 and 1925.[6] Over 90 per cent of the premature infants of the treated patients fell above the upper curves for both weight and length. The scattergrams of control babies, on the other hand, are not significantly higher than the 50 per cent above and 50 per cent below average that would be expected if the upper curves of Ylppö are applicable to babies delivered at the Boston Lying-in Hospital between April, 1947, and January, 1949, the period of this study.

It seems clearly indicated by the above data that the administration of stilbestrol as a prophylactic measure reduces fetal mortality from prematurity largely because the infants are unusually mature for their gestational ages. In other words, it would appear that a better intrauterine environment had been provided than would have pertained if stilbestrol had not been given. Our interpretation would be that the placental secretion of estrogen and progesterone had been stimulated to its maximum capacity up to the time when nonhormonal factors gained the supremacy and brought on the vascular and hormonal deficiency associated with the onset of labor.[3] According to our present state of knowledge concerning the physiological action of the placental steroid hormones, the combined action of estrogen *and progesterone* in adequate amounts would be required to accomplish this result.

3. *Postmaturity.*—

Delivery seventeen or more days after the expected date of confinement occurred in nineteen, *3.4 per cent*, of the control women, with one fetal death, and in four treated women, *1.0 per cent*, with no fetal loss.

4. *Unexplained Stillbirths.*—

Six infants, 1.1 per cent, were stillborn to control mothers; two, 0.5 per cent, to treated mothers. The incidence of this abnormality was very low in both groups and the difference is not significant. Stillbirths that occurred in patients who had pre-eclampsia or eclampsia were considered referable to toxemia and included in that category. All fetal deaths in both control and treated patients that were due to obstetrical accidents (e.g., subarachnoid hemorrhage, strangulation by cord about neck or prolapse of cord) were omitted from this study.

5. *Total Fetal Mortality.*—

In the control primigravidas, five infant deaths were associated with maternal toxemia, nine with prematurity, and one with postmaturity; six were stillborn, making a total of twenty-one, *3.8 per cent*. The deaths of two infants of treated mothers were referable to toxemia; two other babies were stillborn, totalling four, *1.0 per cent*.

6. *Uncomplicated Pregnancies.*—

A. *Mothers*: The uncomplicated gestations of the remaining 330 treated primigravidas were compared with those of the remaining 426 controls to discover whether there were any differences accountable to the administration of stilbestrol. These comparisons included the highest diastolic blood pressure reading during the last month of pregnancy, percentage gain in weight from the time of the first visit, percentage loss of weight after delivery, the duration of the first and second stages of labor, and the incidence of uterine bleeding at term, uterine inertia, and postpartum hemorrhage. No significant difference between treated and control mothers was found in any one of these categories.

B. *Infants*: An unexpected development of this investigation has to do with the weight and length of the babies born to the women who received stilbestrol and had normal gestations. In the first study[1] mention was made of the observation volunteered by several obstetricians that the premature babies from

stilbestrol-treated patients were unusually rugged for their gestational age. Direct evidence in support of this observation has been given above. The explanation appears to be that the drug stimulated better placental function and hence bigger and healthier babies by the time premature delivery occurred. Although stilbestrol was expected to keep more gestations normal, as demonstrated by the material already presented in this paper, we did not anticipate that it could render normal gestation "more normal," as it were. The babies of these treated mothers, however, gave evidence of having been in a better maternal environment, as shown in Tables VI and VII, which compare the weights and lengths of those infants concerning whom these figures were available. There were significantly fewer light infants and significantly more heavier and longer infants.

TABLE VI. DISTRIBUTION OF BIRTH WEIGHTS OF FULL-TERM INFANTS

WEIGHT AT BIRTH	STILBESTROL		CONTROLS	
5 pounds, 9 ounces to 5 pounds, 15 ounces	12	*4%*	30	*8%*
6 pounds to 6 pounds, 15 ounces	77	25%	112	31%
7 pounds to 7 pounds, 15 ounces	146	47%	161	43%
8 pounds or over	76	*24%*	66	*18%*
Totals	311		369	

TABLE VII. DISTRIBUTION OF LENGTHS AT BIRTH OF FULL-TERM INFANTS

CROWN-HEEL LENGTH AT BIRTH	STILBESTROL		CONTROLS	
Less than 19 inches	16	5%	18	5%
19 to 20 inches	103	35%	177	49%
20 to 21 inches	112	37%	120	33%
More than 21 inches	67	*23%*	47	*13%*
Totals	298		362	

That the greater size of more stilbestrol infants was real and not referable to retention of fluid is demonstrated in Table VIII. The initial loss of weight was exactly the same in each group.

TABLE VIII. DISTRIBUTION OF INITIAL WEIGHT LOSSES IN FULL-TERM INFANTS

WEIGHT LOSS IN PER CENT OF BIRTH WEIGHT	STILBESTROL		CONTROLS	
8% or less	64	21%	81	22%
8+ to 11%	139	46%	166	46%
11+ to 15%	74	25%	92	25%
More than 15%	26	8%	26	7%
Totals	303		365	

Seventy per cent of the babies of both groups were breast fed, showing that stilbestrol administration during pregnancy, in the dosages given, had no influence upon lactation. The fact that a greater number of premature infants of stilbestrol-treated mothers were breast fed than of the controls, therefore, must have been referable entirely to the state of the infants.

The question as to whether stilbestrol might salvage a greater number of abnormal fetuses has logically arisen, the greatest concern being for defective ova that would ordinarily abort. In our first stilbestrol study,[1] 491 of the 632 cases reported were started on stilbestrol for threatened abortion or for the prevention of abortions that might have been anticipated. Three hundred and ninety-five of these carried to viability with one fetal abnormality, a case of webbed fingers. This gives an incidence of only *0.25 per cent* as against the *1.0 per cent* incidence of congenital deformities and abnormalities in newborn

infants of the population as a whole.[7] In the present study, one of 387 "stilbestrol" babies had an anomaly, polydactylism; whereas seven of the 555 controls were abnormal, as follows: polydactylism 2, meningocele 2, mongolism 1, hydrocephalus 1, and anencephalus 1. We know of no reason why stilbestrol, started as late as the twelfth week, should reduce the incidence of fetal abnormalities, as might be inferred from these figures. It seems safe to conclude, however, that the use of stilbestrol in the dosages prescribed by us is associated with no risk of maintaining an abnormal conceptus. Moreover, there has been no case (among the total of 1,191 stilbestrol-treated patients in our records) where malignant change in the chorionic elements has occurred, although a number of the abortuses have had hydatidiform degeneration.

Summary

In a clinical experiment aimed at determining the value of diethylstilbestrol in the prevention of the complications of late pregnancy, 387 primigravidous women in the prenatal clinic at the Boston Lying-in Hospital were given the drug in gradually increasing doses from the early part of pregnancy (weeks 12 to 20) to the thirty-sixth week. So far as was possible, alternate primigravidous women who presented themselves for prenatal care before the twentieth week were treated, the synchronous untreated patients, of whom there were 555, serving as controls. Except for stilbestrol administration, the obstetrical care of the two groups was identical.

The incidence of late pregnancy toxemia was very low (*2.3 per cent*) in the stilbestrol-treated patients. The difference between this figure and the *6.8 per cent* incidence in the control series could not have occurred by chance. In the few cases that developed despite stilbestrol, the disease was later in onset and less severe than in the control group.

Analysis of the data on spontaneous premature delivery revealed that the premature infants of stilbestrol-treated mothers were unusually large and mature for their gestational ages. If prematurity is defined in terms of weight of the babies, the incidence of this abnormality was significantly less in the treated patients than in the controls. On the basis of week of delivery, on the other hand, there was no real difference between the two groups.

Postmaturity was significantly less frequent in the stilbestrol-treated patients than in the controls.

The incidence of unexplained stillbirth was 1.1 per cent in the controls and 0.5 per cent in the treated patients. This difference could have occurred by chance.

There were four fetal deaths in the stilbestrol-treated patients, an incidence of *1.0 per cent* as against twenty-one, or *3.8 per cent*, in the untreated patients; a highly significant difference. This reduction in fetal mortality would appear to be due largely to two factors: (1) the lower incidence and later onset of toxemia, and (2) the greater size and maturity of prematurely delivered infants.

A complete analysis of the data on the uncomplicated term pregnancies of the treated and control patients revealed no difference so far as the mothers were concerned (e.g., length of labor, uterine inertia, intrapartum or post-

partum bleeding, weight gain). Analysis of the data on full-term infants, however, revealed that significantly more babies of stilbestrol-treated mothers weighed over eight pounds and were more than 21 inches long at birth.

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Discussion

DR. ERNEST W. PAGE, San Francisco, Calif. (by invitation).—The use of stilbestrol for the prevention or treatment of disease has brought to our specialty one of the most exciting and controversial topics in recent years. Dr. Olive Smith and Dr. George Smith have been among the most astute students and assiduous observers in this field for over fifteen years. Now they preesnt us with a method for rendering a "normal" process "more normal" by the use of stilbestrol. Even though hormones, vitamins, and enzymes are all catalysts which accelerate vital biochemical reactions and therefore have much in common, it is difficult to believe that such a potent drug as stilbestrol will prove to be—like an essential vitamin—necessary for the most successful outcome of normal pregnancies. This point, however, is only philosophical and is not an argument for or against the concept.

The observations presented here have passed the cold scrutiny of a biometrician, and the differences noted, especially in the occurrence of pre-eclampsia and in the size and weight of the premature infants, are hardly within the realm of chance. Two questions remain for discussion; one concerns the "randomness" of sampling and the other concerns the interpretation of the results.

Is it possible that some unconscious factors of selection could have operated in the production of these differences? Does the fact that the control sample is 43 per cent larger than the experimental sample indicate that whatever disturbance occurred in the planned alternation of cases might likewise have disturbed the complete "randomness" of selection? This can be answered only when the experiment is repeated and the results are confirmed by some persistent iconoclast.

But let us now accept these rather startling statistics as wholly valid and consider the concept. Dr. Smith has always emphasized the purely endocrinologic effects of stilbestrol, namely, that it stimulates the placenta to utilize more chorionic gonadotropin and thereby to produce more estrogens and more progesterone. I would like to point out that it may not be necessary to evoke such a concept in order to explain the results. Dr. Smith has referred several times to a secondary disturbance of the blood supply to the pregnant uterus as a factor in producing many of the accidents of pregnancy. It would seem to me that the vascular disturbance is more likely the primary cause for the impaired placental function, for the smaller babies, and for pre-eclampsia. Could not stilbestrol be a drug which exerts its effect directly upon the vascular apparatus and thereby reduces the frequency of ischemia of the gravid uterus? With this as a basis, we may circumvent the objections of some endocrinologists who, correctly or not, claim that stilbestrol does *not* increase the secretion of progesterone, and that an endocrine organ does *not* use a protein hormone during its elaboration of steroids. Most investigators have had the experience of following what later may prove to be erroneous concepts, but still arriving at valid conclusions.

If stilbestrol can prevent interferences with the blood supply to the pregnant uterus, we have not only a rational basis for its use, but a stimulus to investigate the prophylactic

use of other drugs which are not necessarily hormones but which act directly upon the vascular apparatus.

We owe a great debt to Dr. Olive Smith and Dr. George Smith for this stimulating study which represents a prodigious amount of work and a great deal of careful thought.

DR. OLIVE SMITH, Brookline, Mass. (by invitation).—Dr. Page has suggested that the results presented could be entirely explained on the basis of a direct effect of stilbestrol on the vascular supply to the placenta. We find it impossible to sidestep the issue as easily as this, first because we have good reason to believe that estrogen alone in the dosages given could not possibly produce the vascular and myometrial development reflected in the results obtained, and second because recent developments in the measurement of the urinary metabolites of progesterone are confirming our original evidence for the stimulative effect of stilbestrol upon the production of progesterone in human pregnancy.

Drs. Davis and Fugo have recently confirmed our original observation that stilbestrol administration in pregnancy is followed by an increased excretion of sodium pregnandiol glucuronide as measured by the Venning method. They have shown, however, that no rise in pregnandiol excretion after stilbestrol is demonstrable when this metabolite of progesterone is measured on hydrolyzed urine by the H_2SO_4 color reaction. Dr. Marrian of Edinburgh using essentially this same method has reported an actual decrease in pregnandiol following stilbestrol. Drs. Davis and Fugo have jumped to the conclusion that the rise in sodium pregnandiol is due to recovery not of more pregnandiol but of stilbestrol glucuronide. This possibility was considered by us some years ago when Mazur and Shore recovered stilbestrol glucuronide from the urine of stilbestrol-treated rabbits. It was rapidly eliminated on three scores: (1) Sodium pregnandiol glucuronide recovered from the urine of patients taking 150 mg. of stilbestrol daily was added to the urine of surgical castrates, hydrolyzed, and extracted by methods known to recover stilbestrol. The estrogenic activity has amounted to no more than 50 rat units per 100 Gm. of sodium pregnandiol glucuronide. In terms of stilbestrol glucuronide this would represent 15 micrograms per 100 mg. of sodium pregnandiol glucuronide, too little to have any effect at all upon pregnandiol values. (2) The administration of 75 to 100 mg. of stilbestrol daily to nonpregnant patients results in no pregnandiol excretion as measured by the Venning method. (3) We have emphasized the fact that stilbestrol alone is of no value in the definitive treatment of established toxemia, our explanation being that syncytial degeneration once under way is irreversible. As much as 200 mg. of stilbestrol daily does not prevent the steady decrease in the excretion of sodium pregnandiol that characterized both this disease and the termination of normal pregnancy.

The difference between the results by the Venning method and by the color reaction on hydrolyzed urine, therefore, cannot be explained on the basis of recovery of stilbestrol glucuronide. Some other explanation must be found.

Dr. Marrian has isolated pregnanolone from human pregnancy urine as a glucuronide. Dr. Venning reports that pregnanolone is recovered by the Venning procedure and constitutes about 20 per cent of the sodium pregnandiol of pregnancy urine. Dr. Dorfman of Cincinnati demonstrated it in the urine of a man to whom progesterone was given, thus establishing it as an excretory product of progesterone. For the past year we have been trying to put all of these facts together as they may apply to the effect of stilbestrol upon the excretion of estrogen metabolites. On 100 urine specimens from ten different women taking stilbestrol during pregnancy we have measured pregnandiol by three different methods: the Venning method and two modifications of the H_2SO_4 color reaction on hydrolyzed urine, the second of which is our own and eliminates some of the nonspecific chromogens that will give gross overestimates in certain pregnancy urines when this colorimetric test is used. As a result of this study we can make the following statements at this time:

By all three methods an increase in pregnandiol excretion immediately follows the administration of stilbestrol to a patient whose pregnandiol level is just beginning to drop, i.e., a patient in the very early stages of a progressive progesterone deficiency.

A temporary drop in pregnandiol excretion as measured by the colorimetric assay follows the initiation of stilbestrol therapy to a perfectly normal patient. This drop is due, at least in part, to a temporary effect of stilbestrol in lowering the excretion of nonspecific chromogens. It disappears in a few days and is followed by a steady rise. This initial drop is accompanied by an immediate marked rise in the excretion of sodium pregnandiol, this rise being due, at least in part, to an increased excretion of pregnanolone. There is no question, therefore, on the basis of the findings of three independent investigators, all of whose results are in agreement provided they use the same methods, but that stilbestrol is having a profound and immediate effect upon the excretion of progesterone metabolites. And the findings of all three are in keeping with our original hypothesis, namely, that more progesterone is being produced.

DR. OTTO SCHWARZ, St. Louis, Mo.—I was interested in the increased weight of the babies of the stilbestrol-treated patients. I would like to ask the authors whether they watched the birth weight after the initial loss in these babies and compared this in children of controls, indicating that there might be an increase in the fluid rather than in structure in these babies. Is there an increase in amniotic fluid with these babies? I did not hear anything about why these children should have increased weight; however, it may be due to actual increase in circulation due to additional estrogen stimulation.

Recently I examined some forty specimens of pregnant uteri to study the condition of the veins and arteries. I found that at twelve weeks there is marked hyperplasia and hypertrophy of the veins and arteries. This increase continued until about the beginning of the third trimester. The vessels in the third trimester did not decrease in size but histologically there was a change, the active proliferation began to lessen to a considerable degree and the cell structure of the wall was changed back to the more usual type of cell. It may be that when stilbestrol is given this procedure may cause the vessels to keep their patency up sufficiently to cause a definite increase in body weight and in size.

DR. WILLARD M. ALLEN, St. Louis, Mo.—I would remind you of two observations: In the nonpregnant rabbit the administration of estrogen prevents involution of the corpora lutea. The corpora lutea will remain functional for a month or six weeks when estrogen is given whereas they normally function for only twelve to fourteen days. In pregnancy the situation is equally interesting: the administration of estrogen is very deleterious to the fetus. In early pregnancy estrogen will prevent implantation or produce abortion, and during the later stages it leads to death of the fetus. The dead fetuses are not aborted, however, because the administration of estrogen causes the corpora lutea to remain functional. Estrogen will completely suppress the mechanism of delivery. These findings support the theory that estrogens alter the capacity of the corpus luteum to put out progesterone. (G. P. Heckel and W. M. Allen: Endocrinology, 24: 137, 1939.)

There is one other point that may be pertinent. Estrogens do effect the uterine muscle. Estrogen stimulates the uterus of the nonpregnant rabbit to undergo rhythmic contractions. The uterus of a nonpregnant rabbit is responsive to Pituitrin. The administration of progesterone to castrated rabbits makes the uterus nonresponsive to Pituitrin but when exposed to both estrogens and progesterone such a uterus, when suspended in a water bath, shows a very interesting response to Pituitrin; when Pituitrin is added the uterus stops contracting and becomes atonic. The response to Pituitrin is, therefore, conditioned by the type of hormones to which the uterus has been subjected: the uterus under the influence of estrogen responds to Pituitrin by tetanic contractions, the uterus under the influence of both estrogen and progesterone responds to Pituitrin by relaxing.

It seems to me quite probable that the beneficial effects which stilbestrol exerts can be explained by assuming that stilbestrol either enhances the production of progesterone or that it produces a more favorable balance between estrogen and progesterone, thereby permitting relaxation of the uterine muscle so that the uterus itself can better accommodate the growing fetus.

DR. RALPH REIS, Chicago, Ill.—The Drs. Smith have given us a very comprehensive picture of the effect of stilbestrol on the prengant woman and have placed it above the realm of chance. The results show more big babies, fewer premature babies, longer babies, and heavier babies. I must confess at the moment to a degree of bewilderment because with the previous recommendations of the more or less prophylactic use of stilbestrol in diabetics who are pregnant will we not defeat the very purpose and means by which we hope to salvage babies from the pregnant woman who is diabetic? If we give them stilbestrol and they develop larger and heavier and longer babies, where will we end up with our treatment of the diabetic pregnant woman?

DR. GEORGE W. KOSMAK, New York, N. Y.—I would like to have the essayist state what dosage of stilbestrol he uses.

DR. FRED L. ADAIR, Chesterton, Ind.—In connection with this remarkable contribution of the Drs. Smith I want to ask about the effect of the administration of stilbestrol on the placenta from two points of view: the normality of the placenta and the size of the placenta. Both of these might have a direct influence on the development of the fetus. Also, it seems to me that in view of the fact that the placenta and some of its physiologic activity may be related to toxemia of pregnancy, there might be an indirect influence of stilbestrol upon the functioning capacity of the placenta and its normality.

A number of years ago Dr. Hulda Thelander and I studied the relationship between the placental and fetal weight and we found that the volume of the placenta was more important than either the dimensions or weight; that there was a closer relationship between the volume of the placenta and fetal weight than there was between dimensions or actual weight of the placenta. In considering the relationship between the placental and fetal size, volumetric studies by means of fluid displacement would be more valuable than either the weight or dimensions of the placenta.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—The work of the Drs. Smith may prove to be a most important contribution. Their results, presumably due to the administration of stilbestrol, are better than we have been able to accomplish by extensive and expensive prenatal care. I do not know what it is due to. I hope that they will continue their work, to obtain a much larger series, and I also hope that other obstetricians who have large clinic services will undertake this work. As soon as we finish our nutrition project I will propose to the staff that we adopt the plan.

I gather that the essayists have not used a placebo which I think is important. I am also curious as to how they know whether or not the patients take the stilbestrol.

Is there a possibility that the basic radicle of stilbestrol may be the agent producing their good results rather than the estrogenic factor?

DR. GEORGE VAN S. SMITH (Closing).—Dr. Page raised the question of some unconscious selection of patients. We were not trying to sell stilbestrol; we were trying to find out whether our idea was correct. The selection of patients was made by an elderly, retired, primary school teacher; she had had no experience whatever with medical problems; one woman looked just like another to her as regards pregnancy. The reason why we had more controls is simply that in the rushing prenatal clinic it was impossible for one person to select accurately alternate cases; some who would have been treated got by and were later included in the controls.

Dr. Page also questioned the validity of thinking that chorionic gonadotropin is utilized for the production of the placental steroids. That chorionic gonadotropin is so utilized is still a concept which was first advanced by Drs. Browne and Venning of Montreal. We have adopted this concept, thinking it might explain the drop in gonadotropin toward the end of the first trimester, when the steroid hormones increase and when there has been no great decrease in the cytotrophoblasts which produce the gonadotropin. The

slight rise of gonadotropin toward the end of gestation, when the cytotrophoblasts have practically disappeared, we conceive to be due to a failure of utilization by the degenerating syncytium.

Dr. Schwarz asked if the infants of stilbestrol-treated mothers continue to lose weight after their initial loss. Actually our "initial loss" figures represent the *total* loss prior to the increase in weight after delivery.

We were not told by the delivering obstetricians of any increase of amniotic fluid in relation to the use of stilbestrol.

The greater length of more of the babies of stilbestrol-treated mothers is indicative of actual growth rather than of any water retention.

Dr. Reis asked if stilbestrol might make big babies bigger in the diabetic patient. We do not know the answer to that question because our experience with diabetics has been small, but it is safe to say that Dr. Priscilla White has not found that the babies of diabetic mothers treated with stilbestrol were too large compared with the ordinary large baby of diabetic mothers.

Dr. Kosmak inquired about the dosage schedule. This is included in the paper to be published and is practically the same as that already published in the November, 1948, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

Dr. Dieckmann asked about the use of placebos, undoubtedly for its psychologic effect. We have not used them. However, I have felt that the frequent interviews with the interested and kindly school teacher might have been reassuring and done something to help these patients. Dr. Dieckmann also asked about the basic radicle of stilbestrol being the stimulating factor. That was our original idea and our reason for using stilbestrol. From our evidence in studying estrogen metabolism, we think that the stimulating molecule is not estrogenic but that the estrogen is changed and thus becomes a factor which stimulates the secretion of progesterone and estrogen, either through the pituitary gland or through enhancing the utilization of chorionic gonadotropin.

Dr. Wilson inquired when stilbestrol treatment was initiated: 75 per cent of our patients started therapy between the twelfth and sixteenth weeks; the other 25 per cent started therapy between the sixteenth and twentieth weeks of pregnancy.

A STUDY OF THE PLACENTA IN PREGNANCY TREATED BY STILBESTROL*

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As a part of inquiries by Drs. G. V. and O. W. Smith into the effects of stilbestrol therapy in pregnancy, an analysis of weights of babies and placentas in treated and control series has been carried out. Gross and microscopic observations were also correlated in an effort to determine any stilbestrol effect upon the placental morphology. The primiparous full-term material included 188 cases treated with stilbestrol and 92 control cases, all primiparous pregnancies having normal deliveries without late pregnancy complications. Primiparous premature deliveries and toxemias were also investigated and will be discussed later.

Baby weights in 73 per cent of full-term control cases and 58 per cent of stilbestrol cases were between 3,000 and 3,600 grams (6 pounds, 4 ounces, and 7 pounds, 8 ounces). In the weight range over 3,800 grams (7 pounds, 15 ounces) there were 19 per cent of control cases, 27 per cent of stilbestrol cases. This indication of a larger number of heavier babies in the stilbestrol cases is the only finding significantly different in the full-term groups (Table I).

Table I. Percentage Incidence of Full-Term Baby Weights in Kilograms

Weight in kg.	2.4	2.6	2.8	3.0	3.2	3.4	3.6	3.8	4.0	4.2	4.4	4.6
Stilbestrol %	0	3.2	9.2	11.3	11.3	16.2	19.5	11.9	11.3	1.6	1.1	1.1
Controls %	1.1	3.3	3.3	17.6	16.5	22.0	16.5	4.4	6.6	6.6	1.1	0

Comparison of placental weights in the two groups revealed no definite differences (Table II).

Table II. Percentage Incidence of Full-Term Placenta Weights in Kilograms

Weight in kg. below	0.4	0.4	0.45	0.5	0.55	0.6	0.65	0.7	0.75	0.8
Stilbestrol %	1.6	8.1	8.7	21.1	13.0	19.0	12.4	10.0	3.2	2.7
Controls %	1.1	7.8	10.0	13.3	19.0	22.2	13.0	10.0	1.1	2.2

Ratio of baby weight to placenta weight is an index of relative maturity.[1] Comparison of this ratio in the two groups showed no variation indicating any distinct trend (Table III).

Gross and microscopic investigations of the placentas have been tabulated. Relative amounts of subchorionic fibrin deposition, placental calcification, and

*Presented in part, as a discussion of the paper read by the Drs. Smith at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

TABLE III. PERCENTAGE INCIDENCE OF FULL-TERM BABY/PLACENTA WEIGHT RATIOS

Ratio baby to placenta below	4	4-4.5	4.5-5	5-5.5	5.5-6	6-6.5	6.5-7	7-7.5	7.5-8	Over 8
Stilbestrol %	0	1.6	6.0	18.3	22.0	13.4	16.1	11.3	7.0	4.3
Controls %	1.1	2.2	11.1	11.1	14.4	17.7	12.2	7.7	11.1	3.3

hemorrhage were recorded. Presence of significant numbers of immature, mature, and senile chorionic villi was noted. The incidence of the diagnosis of placental infarction, intervillous thrombosis, and nontoxic premature separation of placenta was noted. The findings are compared in Table IV.

TABLE IV. FULL-TERM PLACENTAS

		STILBESTROL (PER CENT)	CONTROLS (PER CENT)
Subchorionic Fibrin:			
Amount:	Small	35	40
	Moderate	46	46
	Marked	9	9
Calcification:			
Amount:	Small	61	67
	Moderate	18	16
	Marked	11	5
Hemorrhage*:			
Amount:	Small	40	54
	Moderate	26	26
	Marked	7	5
Chorionic villi:			
	Immature	17	13
	Mature	82	86
	Senile	1	1
Infarcts		21	17
Intervillous thrombi		25	16
Nontoxic separation		8	11
Circummarginate		27	9
Circumvallate		5	2

*As evidence of premature separation.

Grossly, circummarginate stilbestrol placentas are three times as frequent as found among controls. The only other differences apparent are twice as many cases of marked calcification in the full-term stilbestrol series as among the controls, and more frequent intervillous thrombosis in the stilbestrol group in a ratio of three to two. Both changes are indices of marked aging in some stilbestrol placentas.

Histological study of the whole group of full-term placentas and comparative retrospective analysis have not shown any differences characteristic of stilbestrol therapy in the placenta. It is noted that no stilbestrol was administered during the last three to four weeks before delivery. If a difference existed, it may already have disappeared at the time of delivery. Also, the withdrawal of stilbestrol may have exaggerated placental aging, and encouraged the marked calcification and intervillous thrombosis occasionally observed.

A comparable investigation was made of placentas of twenty-seven premature births, of thirty-eight weeks' or less gestation, with stilbestrol therapy and twenty premature births without treatment. The gestation periods were mostly thirty-five to thirty-seven weeks' duration, and twins were excluded.

Statistical investigation of this group by the Smiths has already shown that premature infants born after stilbestrol therapy are larger than control infants. Comparison of placental weights of twenty-four stilbestrol premature infants

and thirteen control premature births (Table V) showed that stilbestrol therapy was accompanied by increased placental weight. Eighty-four per cent of the stilbestrol series weighed over 400 grams and 54 per cent of the controls.

TABLE V. PERCENTAGE INCIDENCE OF PREMATURE PLACENTAL WEIGHTS IN KILOGRAMS

Weight in Kg.	0.3-0.4	0.4-0.5	0.5-0.6	0.6-0.7
Stilbestrol %	17	42	25	17
Controls %	46	23	23	8

This difference indicates that a heavier, presumably larger placenta is associated with stilbestrol treatment. The ratios of babies to placental weights was compared for the two premature birth groups (Table VI).

TABLE VI. PERCENTAGE INCIDENCE OF PREMATURE BABY/PLACENTA WEIGHT RATIOS

Ratio baby to placenta	4.5	5	5.5	6	6.5	7	7.5	8
Stilbestrol %	17	29	4	25	8	0	4	13
Controls %	8	15	15	0	8	38	15	0

Note that 75 per cent of stilbestrol baby to placental ratios were 6.0 or less, while 61 per cent of control ratios were 6.5 or more. This means that while with stilbestrol the premature baby and placenta are both heavier, the weight increase of the placenta is relatively greater.

Gross and microscopic findings as before were tabulated for the two groups of premature placentas (Table VII).

TABLE VII. PREMATURE PLACENTAS

		STILBESTROL (PER CENT)	CONTROLS (PER CENT)
Subchorionic fibrin:			
Amount:	Small	51	45
	Moderate	29	30
	Marked	7	0
Calcification:			
Amount:	Small	37	35
	Moderate	4	0
	Marked	7	5
Hemorrhage:			
Amount:	Small	51	50
	Moderate	37	20
	Marked	4	0
Chorionic villi:			
	Immature	40	70
	Mature	59	30
	Senile	0	0
Infarcts		26	15
Intervillous thrombi		29	5
Nontoxic separation		0	30
Circummarginate		37	10
Circumvallate		10	10

The most striking statistical differences found are the increased proportion of circummarginate placentas, the relative frequency of mature villi and intervillous thrombi among the premature stilbestrol placentas, and the absence of cases of premature, nontoxic placental separation after stilbestrol. If nontoxic placental separation follows some degenerative change of decidua, then stilbestrol appears to counteract it. Despite earlier maturation of trophoblast, it was not possible to find any specific histologic changes caused by stilbestrol.

A group of eight cases of toxemia of pregnancy occurring with stilbestrol therapy was compared with twenty-one untreated control toxemic cases. Due

to the small number of cases and disparity of numbers, detailed statistical analysis is not possible. The difference in incidence of toxemia with and without stilbestrol therapy may be the most notable discrepancy. Five of seven stilbestrol babies weighed over 2,700 grams (5 pounds, 10 ounces) and nine of twenty-one control babies were in this weight range. In the stilbestrol group, three of seven placentas weighed over 600 grams, while only three of twenty control placentas were as heavy. Relative distribution of ratios of baby weight to placental weight was similar for stilbestrol and control toxemic groups, but no finer interpretation seemed desirable.

Gross and microscopic study was made as noted before. It was of interest that five of eight stilbestrol-treated toxemia cases had circummarginate placentas, and none of the controls, although two of twenty-one control toxemia placentas were circumvallate. Other factors such as subchorionic fibrin, calcification, and hemorrhage occurred with equal frequency and in similar quantities in both groups. Relatively senile syncytial trophoblast and "Tenney changes" associated with toxemia[2] were noted in one-fourth of placentas in each group. Thrombosis of decidual sinusoids was observed in half the stilbestrol-treated toxemia placentas, twice the frequency encountered in toxemia controls. Intervillous thrombi were seen in half the stilbestrol and one-fifth the control toxemia placentas. Infarcts were more common in the stilbestrol placentas in a ratio of five to four. None of these findings appear to demonstrate clear-cut morphologic differences in the stilbestrol-treated cases associated with toxemia, and review of slides from stilbestrol and control groups confirmed this.

Summary

A statistical investigation has been made of effects of stilbestrol therapy in pregnancy upon weights of baby and placenta. Changes in gross and microscopic placental structure due to stilbestrol have also been sought. Stilbestrol-treated and untreated control groups of primiparous full-term and premature births, as well as cases with toxemia of pregnancy, have been included.

Evidence is presented that weights of both baby and placenta are increased in stilbestrol-treated full-term and premature births and in the toxemia group. Ratios of baby weight to placental weight were the same for stilbestrol and control groups in the full-term and toxemia cases, and were decreased in the stilbestrol-treated premature birth group. Stilbestrol stimulates increase in weight and presumably size of both infant and placenta. One by-product of placental overgrowth found is an increased proportion of circummarginate placentas in all three stilbestrol groups, as compared to controls.

Gross and microscopic study indicated more frequent occurrence of marked placental calcification and intervillous thrombosis in full-term stilbestrol-treated placentas. In premature stilbestrol-treated cases there was similarly a higher incidence of mature chorionic villi and intervillous thrombi. No nontoxic premature separations were encountered after stilbestrol therapy. The toxemia cases with stilbestrol therapy more frequently had thrombosis of decidual sinusoids and intervillous thrombi than controls, but the number of such cases was small. No specific histologic change was observed which was attributable to stilbestrol treatment.

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ETIOLOGY OF ECLAMPSIA*†

I. Water Balance

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DESPITE expert unlimited obstetric and dietetic care we have not been able to prevent the development of pre-eclampsia and an occasional case of eclampsia in our patients. The incidence of pre-eclampsia over a period of years has remained relatively constant but the number of severe cases has decreased. The eclampsia is apparently not severe in that there have been no deaths for many years but we have had similar experiences in the past with, sooner or later, death resulting. We believe our improved results are due to early recognition by the doctors and the nurses of too rapid weight gain which results in the patient being referred to the toxemia clinic where she is under expert care. Failure to improve necessitates hospitalization and, after study and treatment for varying periods of time, termination of the pregnancy.

The senior author[1] has been interested in the etiology, diagnosis, and treatment of pre-eclampsia and eclampsia for over twenty-five years and has made many studies during this period. Unfortunately, complete chemical and physiologic studies on the same patients had not been made because of a lack of personnel. It has only been during the past year that a partially complete staff for research has been available. Just recently a beam balance, sensitive to 1.0 Gm. for weighing patients, and an air-conditioned room for reproducing various climatic conditions, has become available. We believe that pre-eclampsia and eclampsia differ only in the occurrence of convulsions and/or coma in the latter condition. We also believe that these conditions are clinical entities peculiar to the pregnant woman.

The senior author[2] some years ago obtained data on the incidence of eclampsia from various parts of the world. There seems to be no doubt that where native people have little association with civilization, the incidence of eclampsia is very low or the condition does not occur. He also showed that a hot, humid climate in the United States was associated with the highest incidence of eclampsia. Theobald[3] reports a very low incidence of severe toxemia in Siam and a very high incidence in Ceylon, both countries having a similar climate.

*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

†This study was supported in part by the Chicago Lying-in 50th Anniversary Research Fund on Eclampsia.

The woman with access to the grocery store has table salt and baking soda in pound containers and uses both freely in cooking and at the table. She eats too much, drinks too little, and urinates and defecates when convenient for her—not when nature signals. Many women worry about finances, marital difficulties, the pregnancy, etc. The primitive native woman has many diseases but she escapes the overabundance of food and condiments, the habits and living conditions of her civilized sister, and she rarely has eclampsia.

Our studies indicate that the periportal hemorrhages, occasional necrosis, or very rare anemic infarct of the liver, are peculiar to the pregnant woman under certain conditions but are not pathognomonic of eclampsia. Likewise, our studies and those by Canny[4] indicate that thickening of the glomerular capillary basement membrane is not characteristic of eclampsia but occurs in a high incidence of pregnant patients. Thus there is no pathologic lesion either in the liver, kidney, or any other organ characteristic of eclampsia.

Several reports[5, 6] indicate that there is no abnormal renal physiology in eclampsia. This is difficult to believe. However, it should be noted that none of the studies were made during the oliguric or anuric phase of the disease.

Various liver function studies[7] show impairment during severe pre-eclampsia and a rapid return to normal after delivery.

The disappearance in some patients within hours after delivery of all signs and symptoms indicates an abnormal physiology of various organs (liver, kidney, brain, etc.) rather than pathologic lesions which would require a much longer time for a return to normal. Likewise the fact that so many various types of treatment result in the same relatively low mortality, providing no drastic procedures are instituted which of themselves entail a high maternal mortality, also indicate that there is no irreversible abnormal physiology present in most eclamptic patients.

Eclampsia only occurs if normal or hydatidiform villi are attached to the uterine wall (either intrauterine or extrauterine). So far as we know there are no reported cases of eclampsia in patients with chorionepithelioma. Improvement takes place early after death of the fetus but a return to the normal only occurs when all the placental tissue is removed.

We question the published reports of patients who are normal one day and within twenty-four hours or less have eclampsia, occasionally terminating fatally. Many conditions can cause convulsions or coma. Some of these reported cases may be due to accidental or intentional poisoning, to essential hypertension, or to some dozen other diseases. When we know the cause of pre-eclampsia and have some positive criteria for the diagnosis, such cases will be even rarer than they now are.

Vasoconstriction does not seem to be the cause of eclampsia because most of the patients have no absolute or relative hypertension at the onset of their pre-eclampsia. If vasoconstriction is the cause then many of these patients should ultimately have a systolic blood pressure greater than 200 mm. Hg and the severity of the eclampsia should parallel the height of the blood pressure. Our experience is that the majority have systolic blood pressures under 200 and, as a rule, less than 180 mm. Hg. Furthermore, these blood pressures are fixed

in that we have not been able to cause any increase by various substances and methods which normally raise blood pressure. The diastolic pressure in the eclamptic and severe pre-eclamptic patient is unusually high, differing from the patient with essential hypertension in whom the diastolic pressure only becomes high late in the disease. The substance causing the vasoconstriction has been assumed to come from the placenta, the kidney, the intestinal canal, the adrenal gland, the pituitary, etc.

Grollman[8] states that it remains to be proved that hormonal aberration is the cause of toxemia and not the result of some fundamental process.

A number of investigators[9, 10] have reported that proper nutrition, implying an adequate amount of protein and of vitamins and not too many calories, has prevented the onset of eclampsia in their patients and some even claim the prevention of pre-eclampsia. We are analyzing the results of a large well-controlled nutrition study in which there was an adequate number of dietitians to properly supervise the patients and calculate diets, and chemical technicians to analyze blood and urine. There was supplementary protein (milk powder or meat) given without charge and yet some of our patients with good nutrition records not only developed pre-eclampsia but one had eclampsia. It is too early to state whether or not we have decreased the incidence of pre-eclampsia by dietary supervision.

Since there are no pathologic lesions peculiar to eclampsia and since the Goldblatt kidney does not produce eclampsia, we believe that animal experimentation is of no value in determining the etiology of eclampsia. We have, therefore, for some years limited our studies to the pregnant patient.

Many investigators believe that there is first a salt and water retention due to an abnormal capillary permeability. Some of the patients develop a hypertension (which may be compensatory), proteinuria, which may be due to edema of the kidney or to vasoconstriction, and a very few have various other symptoms and signs due to cerebral anoxia, again the result of edema or vasoconstriction, culminating in convulsions and coma, or both. This theory seems the most reasonable and is the one which we are now investigating. We are also accumulating other pertinent data. Our purpose is not to bolster up some preconceived idea of the cause of eclampsia.

We do not know the cause of pre-eclampsia-eclampsia but we hope we can determine the etiology, the diagnosis by some chemical or physiologic test, the prevention, and the proper treatment if recognized soon enough. Our studies seem to indicate that pre-eclampsia and eclampsia are a disturbance in the normal physiology of various organs and tissues which, if not too great, readily returns to normal. It could be compared to early shock which is a recognizable condition due to a decrease in the blood volume which, if treated early enough, is easily curable, but if neglected too long becomes irreversible because of pathologic changes and therefore is not amenable to any treatment. Certain cases of eclampsia can last so long that pathologic changes have occurred which cannot return to normal.

Since we have been using procedures which should increase the severity of the case, we have been impressed by the fact that many patients do not get worse

but even improve on such management. We are speculating with the idea that certainly at the onset there is no toxin circulating in the blood in pre-eclampsia but that the condition is merely the result of a body which has not been able to eliminate water, electrolytes, and possibly other substances as it should. In some patients this may be due to an inherent weakness to excrete electrolytes and in such individuals edema may recur with each pregnancy. We have learned that many patients with pre-eclampsia are not in such a delicate balance that the proverbial straw will precipitate eclampsia.

We are making a very extensive study of pre-eclampsia using as many chemical and physiologic measurements as personnel permits. Treatment is not being neglected as various therapeutic procedures are also being tried. If we were attempting to prove some "pet" theory, our investigative work would cost less and would be much simplified. Many analyses are useless on account of labor beginning or being induced for safety of the patient and baby, specimens are lost, or the study proves valueless.

We are determining plasma and extracellular fluid volume. We realize that all determinations, and these in particular, are subject to an inherent error but believe they may show relative changes. We hope to determine total body water. We now have accurate weights in our patients which we consider of the utmost importance. The volume of the lower extremities is being determined to detect water retention. Water, sodium, potassium, chloride, and nitrogen balances are being made. Serum and urine proteins and their fractions are being determined. Renal and liver function studies are made. Liver and kidney biopsies are being obtained when feasible. Hemoglobin, hematocrit, nonprotein nitrogen, urea nitrogen, uric acid, free and combined cholesterol, and other blood constituents are being determined repeatedly in the same patient. We are determining the antidiuretic hormone in serum and urine in certain cases and the urinary corticoids. Certain tissue enzymes and capillary permeability have been determined.

Various procedures such as repeated injections of plasma, of large amounts of purified serum albumin, injections of pitressin, desoxycorticosterone acetate, ingestion of thiamin chloride, of the B-complex, heparin, isotonic and hypertonic solutions of sodium chloride, solutions of ⅙th molar sodium lactate, glucose solutions, and other experimental, diagnostic, and therapeutic measures are being carried out. We have been amazed to find that many presumably pre-eclamptic patients have been able to tolerate the sodium ion, either orally or intravenously, in large amounts without any clinical manifestation as long as they were able to eliminate it in the urine and the chloride intake was less than one gram per twenty-four hours. A very few patients have not only gained weight rapidly but have developed the characteristic findings of severe pre-eclampsia, namely, headache, dizziness, diplopia, decrease in vision, increase in blood pressure and proteinuria, as the result of the overloading with sodium chloride solution. Water alone or in the form of intravenous glucose solution can, if given in sufficient amount, produce convulsions and coma. Injections of solution of posterior pituitary[1] favor water retention and apparently have precipitated the onset of convulsions in patients with pre-eclampsia.

A vast literature[11, 12] has accumulated during the past two decades on the importance of water for the normal functioning of the body. Extracellular water comprises some 20 per cent of the body weight and intracellular amounts to 50 per cent. Furthermore, water is contained in various compartments, namely, the vascular system, the skin, muscle, brain with a fibrous (dura) and bone capsule; the kidney and the other organs, all with capsules. Obviously a positive water balance will cause increased pressure within these various organs including the brain with its bony walls, thus producing many of the serious symptoms and signs associated either with an excess or a decrease in the normal amount of water within or between the cells.

Water is absolutely essential for life. Too much or too little, depending upon the climate, soon produce systemic changes which if continued may terminate in death in a few hours to several days. A failure of water to reach the kidney even though there may be anasarca is more dangerous than absolute dehydration. Edema may be a protective mechanism for a time. These physiologic changes, together with alterations in weight as well as various symptoms and signs, may be obvious within an hour. The longer the abnormality in water balance persists, the greater the changes in the body.

Haldane and Priestly[13] in 1914 noted in experiments on themselves that excessive drinking of tap water could result in dizziness, vomiting, and an unpleasant sense of fullness. If the hydration continues, convulsions, coma, hypertension, anuria, and death will occur. These observations have been made by various observers.[14] Periodic ingestion of water together with repeated injections of posterior pituitary solution have been suggested by McQuarrie[15] and others as a therapeutic test for epilepsy.

The normal kidneys can excrete up to 1200 ml. of urine per hour for a short time but owing to fatigue the diuresis soon decreases to approximately 750 ml. per hour.

A number of investigators[1] using various tests have demonstrated that there is a delayed excretion of water in pregnant patients which is greatly intensified in severe pre-eclamptic patients. Edema of varying degree occurs in approximately two-thirds of normal pregnant patients.[16] Oliguria or anuria are characteristic of eclampsia and persistence of these signs is associated with increasing mortality.

Janney and Walker[17, 18] administered 200 ml. of water every thirty minutes from 9:00 to 11:30 A.M., and compared the volume of urine from 9:30 A.M. to 1:00 P.M. with the average output of 1353 ml. of the nonpregnant normal individual. At term, normal pregnant women excreted only 67 per cent. The average for toxemic patients was 17 per cent. A significant finding was that the horizontal side position gave the highest water excretion throughout pregnancy, amounting to 99 per cent. The Trendelenburg position in the same patient gave 66 per cent, the dorsal position 55 per cent and the sitting position 32 per cent. The studies by Smirk[19, 20] showing that the lower half of the body acts as a water depot, and the observations of numerous investigators on the increased venous pressure due to the arteriovenous leak through the placenta and the pregnant uterus pressing on the abdominal veins, offers a logical explanation why the horizontal side position should give the highest urinary output in the pregnant woman.

Theobald and Verney[21] have studied the urine output during pregnancy. They found that toward the end of pregnancy women secrete an increasing proportion of urine by night so that the night-to-day ratio may exceed unity. Their explanation is that in the upright posture fluid escapes into the tissues and returns only when the individual is at rest in the horizontal position. Muscular exercise of the legs prevent some, but not all, of the filtration. If the fluid thus lost to the tissue by day becomes so excessive that it cannot all be reabsorbed during the night, edema of the tissues, commencing in the lower extremities, will occur.

Bed rest has resulted in some shifting of fluid from the lower extremities but not in complete subsidence. The inflatable suits worn by dive bomber pilots to prevent blackout were loaned to us by the Navy and we could decrease the size of the legs but could not fit them to the thighs of pregnant patients. Pressure bandages are more applicable to the legs than the suits but we have not been able to adjust them to the thighs. It seems fairly certain that an increased pressure about the legs and thighs will decrease the edema.

Robinson, Power, and Kepler[22] devised a "water test" for determining whether or not patients had Addison's disease. We applied this test to a large number of pregnant toxemic patients, not because we thought they might have Addison's disease, but because the adrenal gland is associated with sodium and water balance and certain standards had been established. The test briefly consists of two parts:

1. A comparison of hourly urine specimens after a test dose of water with the urine volume for the preceding nine hours. If the volume of the largest hourly specimen is less than the night urine, the response is positive, that is, Addison's disease may or may not be present.
2. $$\text{Water factor} = \frac{\text{urea in night urine}}{\text{urea in plasma}} \times \frac{\text{chloride in plasma}}{\text{chloride in urine}} \times \frac{\text{volume of largest hourly specimen}}{\text{volume of night urine}}$$

There was so much nausea and vomiting produced by the administration of 20 ml. per kilo body weight that we decreased this amount to an arbitrary 1,200 ml., which was drunk between 7:00 and 7:45 A.M.

The data for patients who had less urine in the morning hourly specimens than in the night urine are given in Table I. Eighty-two per cent of the preeclamptic patients and 48 per cent of those with essential hypertension had an abnormal ratio before delivery, that is, a positive test.

TABLE I. RATIO OF MAXIMUM HOURLY URINE TO NIGHT SPECIMEN. ABNORMAL PER CENT

PRE-ECLAMPTIC		ESSENTIAL HYPERTENSION		NORMAL PREGNANT		NONPREGNANT
ANTE	POST	ANTE	POST	ANTE	POST	
82	35	48	32	33	33	13

Robinson and collaborators stated that if the water clearance factor was more than 30, or if any of the morning hourly specimens were greater than the night urine, the patient did not have Addison's disease. If it was less than 25

the patient probably has Addison's disease provided that nephritis has been excluded. We add that pregnancy must also be excluded. The water factor was abnormal in 40 per cent of the pre-eclamptic patients, both ante partum and post partum. Comparable figures for patients with essential hypertension are 12 and 17 per cent, respectively; for normal pregnant patients 17 per cent and 0, and for nonpregnant 9 per cent. The means are given in Table II. The marked difference between patients with pre-eclampsia and essential hypertension is evident and is primarily due to the low hourly urines characteristic of pre-eclampsia. The means for the pre-eclamptic patients were 24 before delivery and 99 in the same patients after delivery, indicating a marked difference in water, sodium chloride, and urea metabolism. The patients with essential hypertension in pregnancy had a factor of 194 before and 159 after delivery. They could not only excrete water better than the pre-eclamptic patients but had a slightly higher concentration of urea in the urine, and with the lowered blood urea in pregnancy, the factor naturally was greater.

TABLE II. WATER FACTOR

	PRE-ECLAMPSIA		ESSENTIAL HYPERTENSION	
	ANTE	POST	ANTE	POST
MEAN	24	99	194	159
$P_s = 0.9$	16	79	99	93
S.D.	36	200	288	315

$P_s = 0.9$ = indicates that in 9 out of 10 cases the true value of the mean is between these limits.

The hourly urine volume is shown in Fig. 1. The difference between pre-eclampsia and essential hypertension in the ante-partum group is quite marked. Many of the pre-eclamptic patients had either no urine or very small amounts within the first few hours. Some of the hypertensive patients also had small volumes in the first hours but it is possible that our diagnoses were wrong or that these patients had an essential hypertension with a superimposed pre-eclampsia. It is quite obvious that the pre-eclamptic patient, before delivery, has a markedly impaired water metabolism which has shown a marked improvement by the tenth post-partum day. The patients with essential hypertension show a distinct difference from the pre-eclamptic patients in their ability to excrete water. Our data is still being analyzed but it looks as if one could state that if the patient has a urinary output comparable to that found in essential hypertension, she does not have pre-eclampsia. However, if the output is decreased within the limits for pre-eclampsia, she might have either or both conditions.

Typical cases illustrating ante-partum and post-partum urine volumes are given in Fig. 2. Both the patients with essential hypertension had the condition before pregnancy. The pre-eclamptic patients have not been followed through another pregnancy but have all the other criteria which would seem to support the diagnosis.

In addition to the water clearance factor, we obtained the percentage of water excreted in the same period of time by dividing the urine output from 9:00 to 12:00 by 1,200. Fig. 3 illustrates this data. Here again it is quite apparent that a difference exists in the water metabolism in pre-eclamptic patients as compared with the same patients after delivery, with pregnant patients with essential hypertension and with normal subjects.

Odell and co-workers[23] on our service have given pregnant patients 1,000 ml. of 5 per cent glucose intravenously within a twenty-minute period. Urine was collected in six consecutive fifteen-minute periods. They stated that normal pregnant patients, not in labor, excreted 100 to 125 per cent during the second

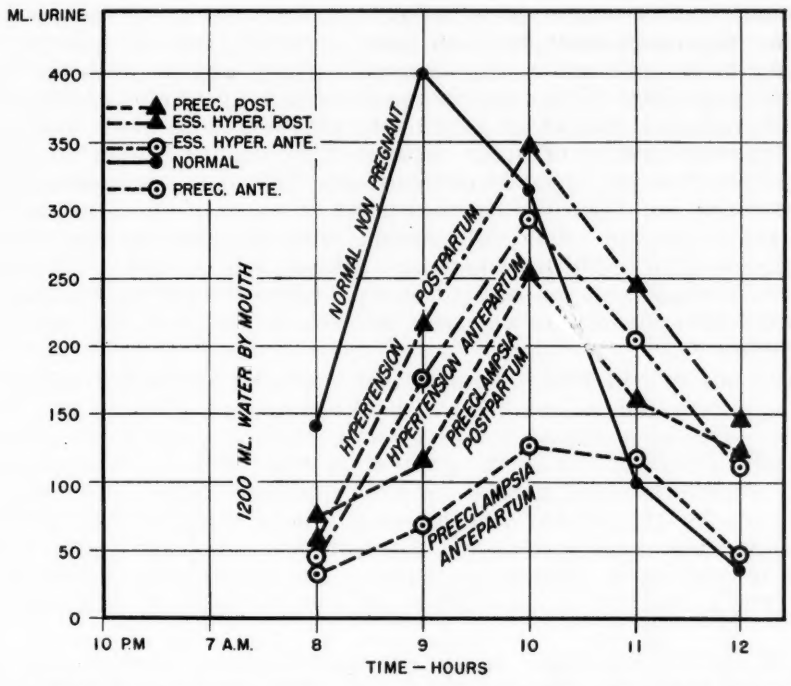

Fig. 1.—Mean hourly urine volume for adrenal function test. Note effect of pregnancy and, in particular, pre-eclampsia in delaying time of diuresis and decreasing urine output.

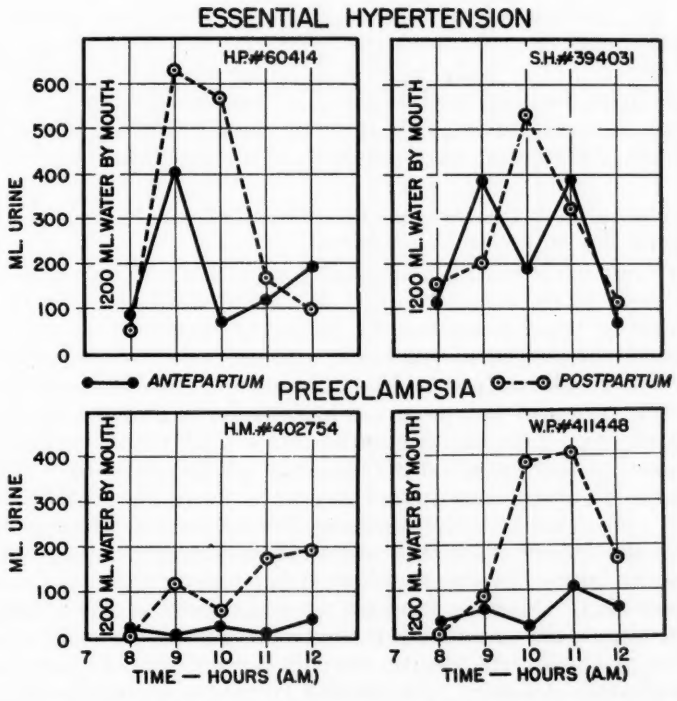

Fig. 2.—Adrenal function tests ante partum and post partum. Note effect of pre-eclampsia before delivery.

urine collection, that is, within 30 minutes from the time of the completion of the injection. Normal patients, early in labor, excreted from 10 to 70 per cent, usually in the third and subsequent periods. Pre-eclamptic patients, not in labor, excreted from 10 to 35 per cent in the third or consecutive periods. Thus, after the intravenous injection of 5 per cent glucose, there is an appreciable decrease in the total amount of urine eliminated, as compared with the normal, and a marked delay in the onset of the diuresis. This study indicates that the delayed excretion is not due to faulty absorption of water in the intestinal tract.

We have all observed eclamptic patients, with no demonstrable edema at the initial examination, within a few hours develop edema of such magnitude that the eyes are closed and the legs pit easily. Since the patient had not been given any fluid, the only source was from her own tissues, where it could have been intracellular.

The senior author[24] in 1940 suggested that "A large amount of water could be held in the muscle cells of the body without the patient showing any demonstrable edema. This phenomenon would account for those patients whose weight gain is so rapid that it must be due to a retention of water and yet no edema can be detected. Furthermore, if this water were quickly released from the cells, it would account for the sudden appearance of edema noted in some eclamptic patients, and for the occasional development of symptoms and signs of acute cardiac decompensation in toxemic patients." He presented a typical case in which there was a negative balance after delivery for sodium, potassium, and chloride.

Thompson and Pommerenke[25] in three pregnant women reported an average retention of 14.7 meq. of sodium and 7.9 meq. of potassium. Coons and coworkers,[26] report a daily mean retention in normal pregnant patients of 0.877 Gm. of chloride, 1.265 Gm. of sodium, and 0.508 Gm. of potassium.

Intravenous injections of deuterium oxide[27] into the guinea pig indicate that 73 per cent of the plasma water is exchanged every minute and that the deuterium oxide comes into equilibrium with approximately 65 per cent of the body weight. Thus water in the body is in a dynamic state; the concentrations of sodium and potassium, both intracellular and extracellular, effect its distribution.

Furthermore, several reports[28, 29] indicate that there are variations in the amount of sodium, potassium, and chloride in intracellular and extracellular fluids.

It is conceivable that the severe type of eclampsia is due to an excessive amount of intracellular water and electrolyte.

Bardeleben[30] cut up a frozen body and found that the legs and thighs comprised 37.2 per cent of the total weight. We have not been able to devise any method for weighing the extremities in pregnant women. Smirk was able to show an increase in the weight of the lower extremities after drinking water and a persistence of the weight indicating that the lower extremities acted as a depot. It is true that the legs and thighs can contain a huge amount of fluid without showing pitting edema. This fluid may be intracellular and we have studies in progress to determine the extent and frequency of this type of water and electrolyte retention. We have been immersing patients to the middle of the thigh in a large metal container and determining the volume by the displacement of water. We find that there may be a decrease in the leg volume by the tenth post-partum day amounting to as much as 6 L., representing a decrease in leg volume of 36 per cent. Various studies[31, 32] indicate that the placenta acts as an arteriovenous shunt, thus accounting for the increased venous pressure in the legs which begins at the fourth month, reaches a maximum at term and rapidly returns to normal after delivery. In the last trimester of pregnancy the venous pressure in the lower extremities is much greater because of the added pressure of the pregnant uterus on the large abdominal veins.

The average venous pressure in the legs at term is 20 cm. and for the arm veins is 9 cm. of water. Landis[33] has shown that fluid accumulates in the tissue spaces when the venous pressure is greater than 15 to 20 cm. of water. A certain amount of protein leaks through the capillary walls, returning to the circulation by the lymphatics. Drinker[34] reports that fluid from a leg lymphatic of a dog contains 0.5 to 2.1 Gm. per cent protein. Protein in the interstitial fluid would attract more water and delay its absorption. Thus, on simple physiologic grounds one can account for a large retention of fluid in the normal depots where reabsorption is delayed in the normal individual. Since the accumulation of extracellular water is accompanied by a retention of sodium and chloride and a probable intracellular retention is accompanied by a retention of sodium, potassium, and chloride, the so-called physiologic edema of most pregnant patients can be accounted for. Studies reveal that some subjects require a longer period to eliminate given amounts of water, sodium, and chloride.

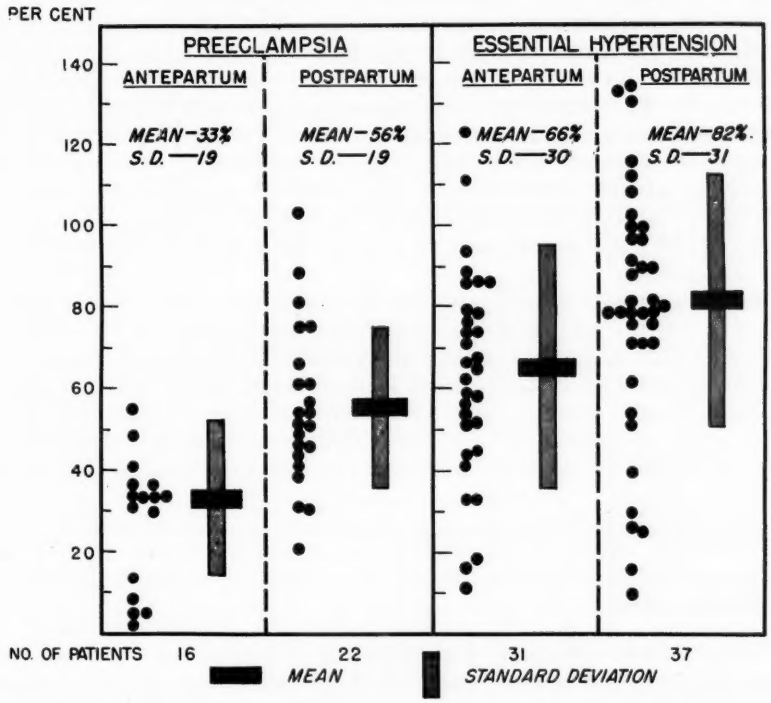

Fig. 3.—Means standard deviations and frequency distributions for percentage of water excreted. Note low figure for ante-partum pre-eclampsia and marked scatter, as well as large, standard deviation.

Any abnormal condition which interferes with water or cellular metabolism will intensify the normal delay in water and electrolyte excretion. Some of these factors are anemia, a slight decrease in the concentration of serum albumin, multiple pregnancy, polyhydramnios, cardiac disease, etc.

The stimulus to urinary secretion of water is an excess amount in the blood of water or of one of the electrolytes or nonelectrolytes. The excretion of water by the kidney is dependent upon a relatively abrupt blood dilution and a decrease in the concentration of the antidiuretic substance (A.D.S.) in the blood. Hart and Verney[35] conclude that a fall in the concentration of the antidiuretic substance of less than one part of substance in fifteen billion parts of the plasma will result in a spontaneous diuresis. Verney[36] states, "Water diuresis is a condition of physiological diabetes insipidus, and there can be little doubt that the

antidiuretic secretion of the neurohypophysis is a hormone in the physiological sense, that its liberation is mainly and continually governed by the contemporary concentration of sodium chloride in the carotid arterial plasma. Changes within the range and of the order of 1 per cent in the osmotic pressure of the arterial blood lead, through the intermediation of the A.D.S., to changes in the rate of water excretion within the range and of the order of 1,000 per cent: the maintenance of near constancy in the osmotic pressure of the internal environment is thereby achieved.''

Verney states, ''The post-pituitary A.D.S. is released in the living animal by two distinct agencies, emotional stress and an increase in the osmotic pressure of the arterial blood. On the assumption that the A.D.S. in post-pituitary extract has, on reaching the kidney, the same structural form as has that released endogenously, this release is shown to be inhibited or suppressed by an increase in sympathetic activity associated with the animal's discomposure.''

According to Smith,[37] the evidence is not conclusive but apparently the major portion of the reabsorbed water due to the action of the antidiuretic substance takes place in the thin segment of the kidney tubule. If the antidiuretic substance is in excess, the excretion of ingested or parenterally injected water is delayed from two to ten hours and it produces a slight and variable increase in the excretion of chloride. It is incapable of accelerating the reabsorption of water if the concentration of salt in the urine is very great. Verney has shown that the membrane of the osmoreceptor is a selected one in that certain substances, for example, sodium chloride, produce a marked secretion of antidiuretic substance while other substances such as glucose and urea produce little or no secretion.

Smirk, in an ingenious experiment in human beings, has shown that after the ingestion of 1,000 ml. of water an increase in the weight of the abdomen is observed, at once followed by a gradual decrease. It requires from twenty-two to fifty-five minutes for the absorption of 1 L. of warm water which occurs best about three hours after a meal. His experiments also show that the weight of the leg and the thigh increase after the ingestion of water and that there is a lag in the decrease in weight of the lower extremity indicating that the lower extremities have acted as a depot.

Various reports[38, 39] indicate that the hormones of the adrenal cortex and thyroid gland, through effects on electrolyte and water excretion, renal function, permeability, etc., have an important regulating influence on the metabolism and distribution of body water.

The pregnant woman has a delayed excretion of water, sodium, and chloride which may be due in part to the increased deposition and delayed absorption caused by the high venous pressure in the lower extremities as well as to changes in the pituitary and adrenal hormones. Our preliminary studies seem to indicate that if there is a constant diuresis, thus preventing any stimulus for the release of antidiuretic substance, the urine volume will remain fairly constant. However, if the antidiuretic substance increases, there is a delay in the normal individual which becomes exaggerated in the toxemic patient, thus accounting for the oliguria or anuria. Other factors may be involved in the decreased excretion of urine but it seems most probable that the antidiuretic substance is the important one. Additional evidence is found in several reports which show that the parenteral injection of solution of posterior pituitary results in the smallest volume of urine per hour, frequently even an anuria of several hours' duration, in patients with pre-eclampsia. We have not been able to find any data as to the mechanism by which alterations in concentration of the antidiuretic substance occur.

Newburgh[40] demonstrated that the optimum amount of urine requiring the least work for the normal kidney is approximately 2,000 ml. per twenty-four hours. He did not state whether the major portion of this urine should be excreted in a few hours or over a major portion of the day. Several observers have reported that the quantity of water lost in a diuresis due to water excess may be greater than the quantity taken in.

Wolf[41] has had ten normal subjects drink 20 to 200 ml. of water per ten-minute periods for as long as seven hours. The urinary output alone was 8 per cent greater than the intake.

The data in Fig. 4 on W. J. D. demonstrates that the excretion of water, sodium, urea, etc., can be maintained at a higher level with a greater total elimination for twenty-four hours if measured amounts of water are ingested at hourly intervals. Incidentally, the subject is much more comfortable under this regime.

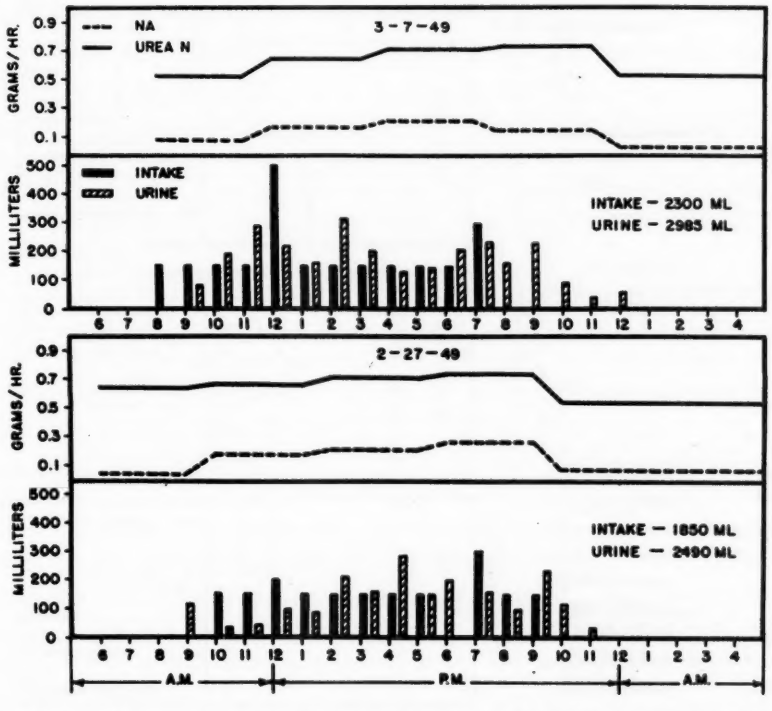

Fig. 4.—Water, sodium, and urea nitrogen balances for two days on subject W. J. D. Note increased output during periodic ingestion of water.

S. S. No. 452429, for whom pertinent data are given in Fig. 5, is a typical case of pre-eclampsia. Unfortunately, but probably best for her safety, she went into labor before our studies were completed. She was able to excrete sodium, chloride, and water while taking fluids at regular intervals Fig. 5 (day 1), but when left to her own choice the intake and output decreased to dangerous levels (days 7, 8, 9, 10). It is quite obvious that if such a course of events is continued for some days there will be a marked accumulation of water and electrolyte in the interstitial spaces and the beginning of a vicious circle (further increases in the venous pressure, edema of kidney, increased cardiac work) which causes a still greater delay in water and salt elimination. Intravenous glucose, even in 5 per cent concentration, produced a diuresis and an increase in sodium, chloride, total electrolyte, urea and nonprotein nitrogen excretion. The diuresis and elimination of retained water and electrolyte which began within forty-eight hours after delivery is typical of

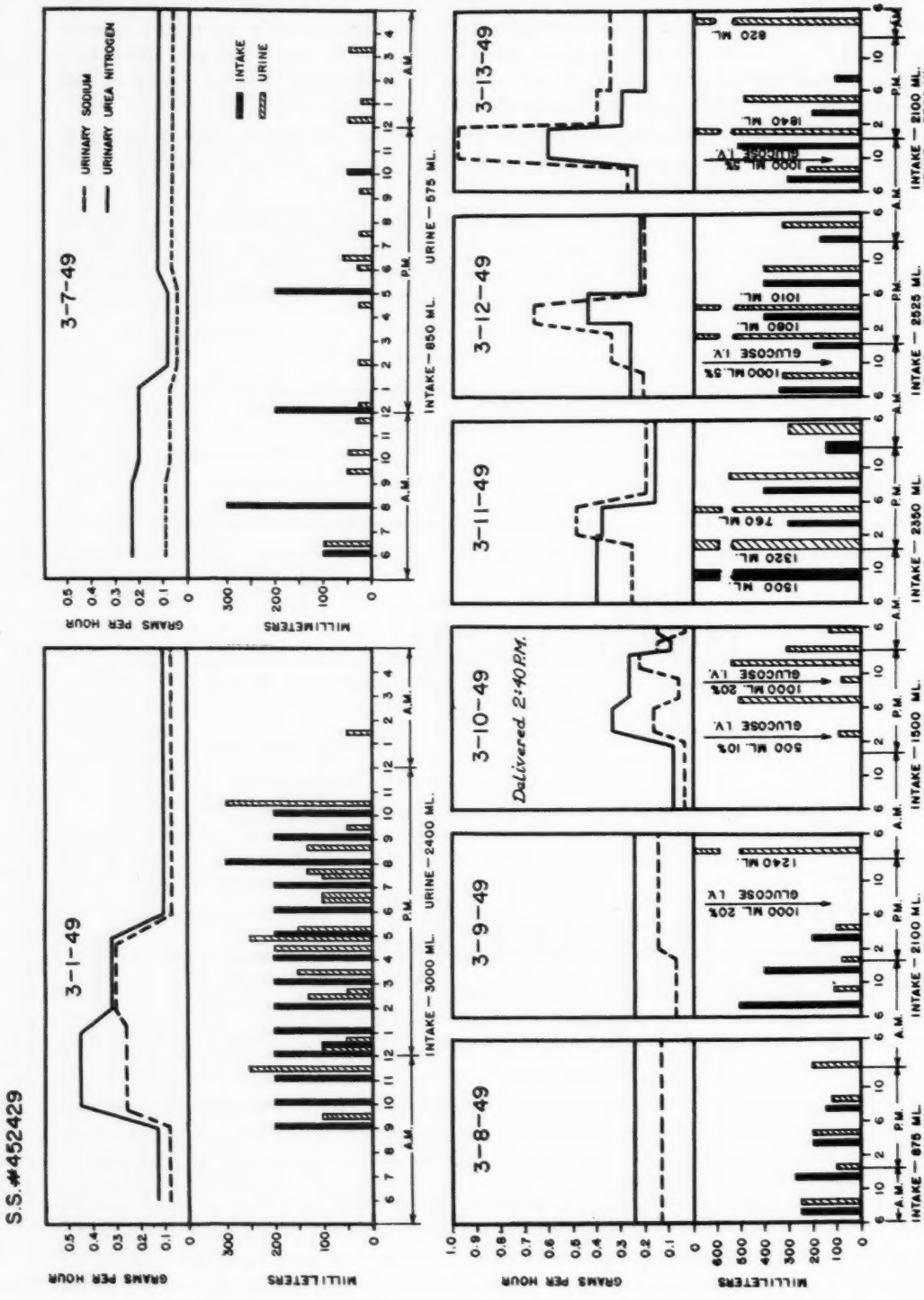

Fig. 5.—Water, sodium, and urea nitrogen balance on pre-eclampsia patient. Note increased output during regulated water intake as compared with markedly diminished output of all substances when patient drank as she desired, culminating in a marked oliguria.

these cases (days 11, 12, 13). The delivery results in a marked and immediate decrease in the venous pressure in the lower extremities where large amounts of water and electrolyte have been retained, thus making these substances readily available for excretion.

We believe that there is sufficient evidence indicating that where there is evidence of extensive peripheral edema, there is also an increased amount of water in the kidney with its tough capsule, thereby probably adding an additional impediment to renal work. The amount of water in the liver is presumably also increased with a resultant impairment in its function to detoxify substances absorbed from the intestinal canal and brought to it from other portions of the body. An increased amount of fluid both inside and between the brain cells may have quite drastic results. One effect may be an increase in the amount of antidiuretic substance or a failure in its removal or neutralization. A small increase in the intracellular or extracellular fluid of the brain will result in an increased irritability and other symptoms and signs associated with anoxia of the brain, namely, headache, dizziness, diplopia, nausea, and vomiting which may terminate in convulsions. A still greater increase will result in coma, hyperpyrexia, and death.

We have studied three pregnant patients with diabetes insipidus who, while not taking pituitary solution or powder, developed edema of the legs. Two had marked edema and hypertension despite volumes of urine ranging from 3,000 to 6,000 ml. per day. Immediately after delivery the edema and hypertension subsided rapidly.

The plan of prophylaxis and of treatment based on Newburgh's observation and our own studies indicates that the pregnant woman should ingest sufficient tepid or cool water with a low sodium, chloride, and potassium content every hour throughout the day and evening in sufficient quantities to yield approximately 2,000 ml. of urine in twenty-four hours. Obviously, in hot, dry weather, she will have to drink more than in cold weather. She should also be taught to decrease the amount of sodium, chloride, and potassium ingested in her food because once these substances are in the body there is some delay in their excretion, even by the normal individual. The maximum concentration of sodium, chloride, or potassium in the urine is 0.7 per cent, 1.1 per cent, and 0.5 per cent, respectively. A normal adult will excrete approximately 5 Gm. of sodium, 11 Gm. of chloride, and 3 Gm. of potassium in the twenty-four-hour urine.

Schwarz and Dieckmann[42] in 1929 stated that intravenous injections of 20 per cent glucose solution would produce an increased excretion of chloride in the urine. We have sufficient data now to show that if enough glucose solution is administered intravenously, the total amount of sodium per hour is definitely increased. Several observers have reported that in nonpregnant subjects intravenous glucose administration will produce an increased elimination of sodium. Stewart and Rourke[43] have shown that the continuous intravenous injection of 5 per cent glucose solution to relatively normal post operative patients over periods ranging from 36 to 144 hours not only resulted in an increased elimination of sodium in the urine but caused a diminution in the volume of the extracellular fluid of 1,960 ml. in one patient. One patient actually became comatose because of the decreased concentration of sodium in her blood and tissues. In other words, she suffered from water intoxication although she was dehydrated. Another patient was given 0.9 per cent sodium chloride with a

7 kg. increase in weight and an increase in the interstitial fluid of 9,870 ml. and of 1,722 ml. in plasma volume without any evidence of edema. This same patient had a maximum decrease of 23 per cent in the plasma protein concentration and a 21 per cent increase in the total amount of circulating plasma protein, thus indicating that there are stores of plasma protein presumably in the interstitial fluid.

These observations of Stewart and Rourke indicate a possibly new type of therapy for the markedly edematous patient, namely, a continuous injection of 5 per cent glucose solution for several days or longer.

Summary

We have not been able by obstetric and dietetic care to reduce the incidence of pre-eclampsia or prevent the development of an occasional case of eclampsia.

The elimination of water given by the oral or intravenous route is delayed in all pregnant patients but more markedly in those with pre-eclampsia than in those who have hypertensive disease. This delay may be due in part to the increased storage of the water in the legs and thighs as a result of the high venous pressure in the lower extremities due to the pregnancy.

The antidiuretic substance from the posterior pituitary and the hormones from the adrenal cortex are also involved but the mechanism of control is still in doubt.

A urinary volume of 2,000 ml. per twenty-four hours is recommended as requiring minimal work by the normal kidney. The hourly ingestion of water in constant amounts of 150 to 200 ml. seems to produce better elimination of water, electrolyte and nonelectrolyte substances than the irregular ingestion of large amounts.

It seems advisable to instruct normal patients not to ingest more than 1 to 2 Gm. of sodium, 4 to 6 Gm. of chloride, and 1 to 2 Gm. of potassium per twenty-four hours during pregnancy.

We wish to thank Miss F. Dunkle (Chief dietetian) and the various residents, nurses, and technicians who have assisted in the various studies and experiments.

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Discussion

DR. W. T. POMMERENKE, Rochester, N. Y. (by invitation).—Those of us who know Dr. Dieckmann and have had the privilege of hearing his presentation are aware of the fact that for years he "has been living intimately with the toxemias of pregnancy." Therefore his comments, born of this long association, are deserving of serious consideration.

Specific predictions in medicine are frequently hazardous. Dr. Dieckmann hints—with a voice that is perhaps too faint—that factors which some may regard as psychosomatic and sociologic may be operative in the etiology of eclampsia. I venture the prediction that we will hear more concerning this aspect of the practice of medicine in the years to come. Many will regard as novel the view, as again expressed by Dr. Dieckmann, that there are no renal or hepatic lesions pathognomonic of eclampsia. Repeated needle punch biopsies of the liver and kidneys should in time establish the validity of this belief.

Researches on the so-called toxemias of pregnancy have been historically linked with and bottlenecked by the search for some phantom toxin. Dr. Dieckmann suggests that pre-eclampsia and eclampsia may have their bases in a deranged physiology rather than in frank pathology. New technologies may, therefore, be expected to furnish necessary information on which to base proper concepts of this disease, or shall we call it "metabolic state." Of these Dr. Dieckmann speaks with enthusiasm and hope.

Would it not be ironic if the long-sought toxic substance turned out to be water? Certainly the immodest imbibition of water by man and beast will produce symptoms, even convulsions, presumably due to cerebral edema, which we associate with severe toxemia.

Pregnancy is a period of rejuvenescence and of growth. It is characterized by storage of large quantities of nitrogen, electrolytes, and water. Let the philosopher argue the import of this storage. The fact is that chemical analyses seem to indicate that this storage is far in excess of actual needs for tissue construction of the fetus.

Water balance studies must take into consideration, in addition to obvious water taken in as such and the quantity of urine eliminated, the fact that there are other significant quantities of water intake and output. The water in food, measurable by dehydration, and that found within the body by the oxidation of fats, carbohydrates, and proteins

should also be reckoned as intake. Furthermore, large quantities of water leave the body by way of the lungs and skin. These items of intake and output may amount to over a liter per day.

But even disregarding these niceties of precision it is apparent that water is stored. Hydremia, inordinate gain in weight, and suppression of urinary output is gross evidence of this water storage. As much as 6,000 c.c. of water can be stored without gross evidence of edema. Edema, therefore, is obvious evidence of even greater storage of water. The legs can thus become veritable reservoirs of water as well as fat.

Bcause the amount of water stored, notably the edema, is often seemingly out of proportion to other clinical manifestations of toxemia, and because with some patients having severe toxemia, edema may not be a conspicuous feature, I wonder if Dr. Dieckmann would care to comment further on any parallelism between the degree of edema and the severity of pre-eclampsia.

One other question: if failure to eliminate water adequately is a feature of pre-eclampsia, would one not wish to consider the use of stronger diuretic measures than the administration of some 2,000 to 2,500 c.c. of water per day?

DR. J. ISFRED HOFBAUER, Cincinnati, Ohio (by invitation).—For the past few years the primary significance in the etiology of late toxemia of pregnancy of the remarkably altered endocrine pattern was put in clear perspective. The demonstration of the occurrence during the last trimester of gestation of a distinct increase in the number and secretion of basophils in the adenohypophysis, hypertrophy of the adrenal cortex with urinary excretion of corticoids in the order of amounts found in the urine of individuals suffering from Cushing's syndrome, increased response of the arterioles to the postpituitary principle and to adrenalin entail potential hypertensive factors, while the vasodepressor effect of placental acetylcholine apparently represents the neutralizing principle concerned with the maintenance in normal gestation of a delicately balanced blood pressure equilibrium. In toxemia, due to significantly higher placental cholinesterase levels and its resulting low acetylcholine content and choline deficiency in the blood, a dislocation of the balanced opposition of contrary stimuli on the vasomotor function ensues, with hypertension as the main sequel.

It is now an accepted fact that hormones play important parts in water metabolism and in the exchange and function of sodium, chloride, and calcium. As an early manifestation of choline deficiency, impairment of the oxidative metabolism occurs (Abdon and Berglin) and, according to a recent announcement by Best, choline deficiency may be an etiologic factor in the mechanism of hypertension. Direct association of heightened activity of the adrenals as playing a genetic role in toxemia is suggested by last year's report of a significant increase in the urinary output of corticosteroids. Recent identification in three pre-eclamptics of our series of nonadrenalin assumes particular interest in view of the demonstration by Bulbring and Burn that splanchnic stimulation can result in the liberation of this power transmitter of constrictor impulses.

DR. GEORGE VAN S. SMITH, Brookline, Mass.—Dr. Dieckmann's paper again brings to my mind the same thought I have had for years: that there is an analogy or similarity between normal pregnancy and toxemia and the phenomenon of menstruation. For years I have puzzled as to what morphologic similarity there could be between these processes. Dr. Hertig has recently given me the answer. He states that decidual necrosis is a constant feature of human gestation, normal and abnormal. This means to me that a menstrual-like process plays a role in normal and abnormal pregnancy. Although Dr. Olive Smith and I have become associated with the idea of abnormal hormonal balance in relation to toxemia, actually our thinking is in terms not of hormones but of the menstrual phenomena.

I would inject another thought. We know that once the uterus is removed from the nonpregnant woman, normal ovaries being left, there are no signs to indicate changes in ovarian hormonal levels. Very little objective study has been done on such women but what has been done gives no evidence of ovarian hormone withdrawal in the absence of the endometrium. In other words, it is not the hormonal withdrawal which ultimately

accounts for the systemic changes of menstruation but the ensuing endometrial catabolism. By analogy, decidual catabolism probably accounts for many of the normal and abnormal systemic changes in pregnancy.

DR. DIECKMANN (Closing).—We believe animal experimentation in pre-eclampsia-eclampsia is of no use. We are concentrating our studies and our experimental procedures on pregnant patients. We have no pet theories which we are trying to prove. We are not making many endocrine studies. I hope the staff will be willing to take up the use of stilbestrol according to the Smith method.

Dr. Pommerenke mentioned the effects of water. There is sufficient evidence now available which shows that too much or too little water is very definitely dangerous to life. The entire syndrome of pre-eclampsia-eclampsia can be produced by giving too much water or by large amounts of water and sodium chloride. A small amount of solution of posterior pituitary will hasten the development of the clinical condition. There are other factors. We do not think that pre-eclampsia-eclampsia is merely water intoxication. Furthermore, every pregnant woman who has convulsions or coma does not a priori have eclampsia. There are over a dozen conditions that have caused convulsions and/or coma in both pregnant and nonpregnant women. All obstetricians have had patients who either gained or lost tremendous amounts of weight (20 or more kilograms) and yet have shown no edema. We believe that patients can have abnormal retention of water and electrolytes without clinical edema. Our studies were all started in the post-partum period, and as we have gained familiarity, the various experimental procedures have been instituted in the ante-partum period.

(The remaining papers presented at this meeting will be included in the December issue.)

Department of Reviews and Abstracts

Selected Abstracts

Newborn

Fox, M. J., Krumbiegel, E. R., and Teresi, J. L.: Maternal Measles, Mumps, and Chickenpox as a Cause of Congenital Anomalies, The Lancet, page 746, May 15, 1948.

Various clinical studies have shown that congenital anomalies (cataract, heart disease, deaf-mutism, and dental abnormalities) follow early pregnancy rubella at fifteen times the ordinary rate. The only other virus effect thus far investigated is that of poliomyelitis, fetal anomalies being present in two infants of 98 cases collected. Both of these cases followed poliomyelitis in the first four months of gestation, of which there were 24 cases in all.

In a survey of sixty thousand cases of measles, mumps, and chicken pox occurring in Milwaukee in 1942 to 1945, the authors found six cases of measles, twenty-three cases of mumps, and four cases of chicken pox in pregnant women. Only one of the thirty-three infants had an anomaly; a congenital harelip following measles in the fourth month of pregnancy. This series is admittedly too small to prove anything, especially since only four patients were infected during the first eight weeks of pregnancy. From a negative standpoint, it is disclosed that 76 children, conceived from three weeks to four years after one of these diseases, had no malformations. Conception soon after rubella, however, has been reported to eventuate in defective infants. IRVING L. FRANK.

Swan, C.: Rubella in Pregnancy as an Aetiological Factor in Stillbirth, The Lancet, page 744, May 15, 1948.

Questionnaires answered by 760 mothers of stillborn babies disclosed that 16 of these women had had German measles during pregnancy, two having also had mumps, and a third chicken pox in the same pregnancy. No other infectious disease had a comparable incidence in these ill-fated pregnancies. In seven of the sixteen cases there was no known lethal factor present. Most significantly, in 13 of the cases, rubella had occurred during the first four months of pregnancy, the so-called "critical period." It is, therefore, suggested that rubella in early pregnancy may cause damage to the embryo eventuating in stillbirth. IRVING L. FRANK.

Unsigned Editorial: Foetal Death or Defect From Maternal Infections, The Lancet, page 760, May 15, 1948.

German measles during early pregnancy often is followed by fetal defects such as cataract, heart disease, deaf-mutism, and dental and mental abnormalities. A cataract is likely to follow infection at six weeks of pregnancy, deafness at nine weeks, and a cardiac abnormality at five to ten weeks. That these defects follow infection in early pregnancy suggests a specific effect of the virus on the developing embryo.

Reliable estimates of the probability that defect, abortion, or stillbirth will follow German measles are essential in deciding the advisability of therapeutic abortion. Swan suggests compulsory notification of *all* infectious diseases occurring in pregnant women, interroga-

tion of women presenting themselves at prenatal clinics, and a close follow-up of all pregnancies complicated by infections. The studies of Ober et al. indicate that rubella in the first month is followed by defect, abortion, or stillbirth in four out of five cases, four out of eight in the second month, three out of nine in the third month, and four out of twenty-seven in the last five months. IRVING L. FRANK.

MacMahon, H. Edward: Congenital Alveolar Dysplasia of the Lungs, Am. J. Path. 24: 191, July, 1948.

The author describes a pathological entity involving the lungs of some full-term newborn infants showing respiratory distress and progressive intractable cyanosis. While the correct diagnosis in such cases is usually atelectasis, the primary congenital anomaly described in this paper can produce the same clinical syndrome.

Three cases are presented. In each instance the child cried and breathed promptly. There was progressive cyanosNis and respiratory distress until death supervened. At autopsy the lungs were normal in size, firm, rubbery, and dark red. The main microscopic change was a predominance of interstitial tissue with far too few alveoli. The interstitial tissue failed to show well-developed mature collagen when stained with Mallory's and fuchsin-aniline blue stain. L. M. HELLMAN.

Ellis, Richard W. B.: The Newborn: Some Problems of Survival, Edinburgh M. J., page 321, June, 1948.

This paper deals with some of the factors concerned with infant wastage in Scotland. The author states that never before has the newborn received more consideration than he does in most civilized countries today. This has been brought about by the fact that the reduction in total infant mortality rate has been principally due to a reduction in death rate of infants from 1 to 12 months of age. The reduction in the death rate of infants under one month has shown very little change from 1911 to 1946. The ratio of neonatal to postnatal deaths for the quinquennium, 1911 to 1914, was 43:71. In 1946 this ratio was 26:26. The better survival rate of females over males is pointed out. The higher infant wastage rate in illegitimate births is considered. Certain factors which may improve this infant loss in this group are discussed. These are improvements in the birth certificate so that the illegitimacy of the infant is not disclosed and improvement in the adoption laws. The question of inoculation of children born to tuberculous mothers with B.C.G. is discussed. A discussion of antenatal, neonatal, and postnatal mortality rates in 1939 and 1945 by social class is presented. It is interesting that the difference in stillbirth rate between social classes was greater in 1945 than in 1939. The question of diet in its relation to the status of the newborn infant is discussed. Some of the current literature is cited. The major causes of infant death are ascribed to prematurity, neonatal infection, intracranial hemorrhage, and congenital malformations. L. M. HELLMAN.

Luschinsky, H. L., and Singher, H. O.: Identification and Assay of Monamine Oxidase in the Human Placenta, Reprinted from Arch. Biochem., vol. 19, no. 1, Oct., 1948.

Monamine oxidase is contained in the human placenta at term. The authors prove the presence of this enzyme by a study of substrate specificity, the demonstration of the reaction products and the action of certain inhibitors. The authors state that, theoretically, about 0.7 Gm. of tyramine can be deaminated by the average placenta per hour. They state that it is probable that the monamine oxidase serves in the detoxification of amines and that, inasmuch as some of the amines are sympathomimetic in their vasomotor action, monamine oxidase in the placenta may separate the fetal from the maternal vasoactive substances and conversely the mother's from those of the fetus. Inasmuch as the activity of this enzyme depends upon partial pressure of oxygen, it may be permissible to assume that under conditions of placental ischemia the enzyme may not fulfill its physiological role, i.e., the destruction of vasopressin amines. L. M. HELLMAN.

Complications of Pregnancy

Bazan, J., Uranga Imaz, F. A., and Fernandez, J. A.: Acute Leukemia and Pregnancy, Obst. y ginec. latino-am. **7:** 145-164, May, 1948.

The authors describe in detail a case of acute myelogenous leucemia in a 24-year-old woman who was five months pregnant. Her leucemia was initiated with an abrupt clinical onset—serious and rapidly progressive anemia, irregular febrile course, ulceration of tonsils, pronounced capillary fragility, gingival hemorrhage, slight hepato- and splenomegaly and ultimate loss of vision. A therapeutic abortion and supportive therapy failed. The patient died two and one-half months after interruption of pregnancy.

The authors, after an extensive review of eighty-eight cases in the world literature, conclude that leucemia is a contraindication to pregnancy and that management of such cases is the joint responsibility of the obstetrician and the hematologist. CLAIR E. FOLSOME.

Portes, L., and Granjon, A.: Amniotic Puncture and Amniography, Gynec. et obst. **47:** 42-48, 1948.

Portes and Granjon, of Paris, do not consider the puncture of the amnion, via the abdominal transcutaneous route, dangerous, while providing certain advantages in selected instances. The removal of excessive liquor amnii in acute polyhydramnios permits the carrying of pregnancy up to a more suitable period of viability of the fetus. In selected cases of therapeutic abortion, the addition of artificial serum, 300 to 600 c.c., to the amniotic cavity is recommended. The changing tonicity of the fluid content with increasing pressure initiates onset of labor. In cardiac, tubercular, and renal contraindication to pregnancy the authors find this method less traumatic than interruption from below. Similarly, the onset of labor, in cases with dead fetuses in utero, can be hastened. If labor does not begin within forty-eight to seventy-two hours, a second amniotic intracavitary injection is given of 200 to 300 c.c.

For amniographic studies the authors use a 20 or 40 per cent aqueous iodized solution as used in urography. These solutions are diluted with artificial serum and injected with a 50 c.c. syringe. Under the fluoroscope the authors have used the amniographic shadows to study uterine contractility and incidentally the action of certain pharmacodynamic drugs upon uterine contractility. The injected iodized solution was eliminated rapidly in the urine of the mother. Four pictures of roentgenograms are included in the article. CLAIR E. FOLSOME.

Ledesma, Domingo: Colpocytology in Hyperemesis Gravidarum, Bol. Soc. de obst. y gynec. de Buenos Aires **27:** 23-26, April 15, 1948.

The author, upon the premise of Anselmino's that hyperprolanemia frequently accompanies a deficiency of estrogen in degenerating moles, chorionepithelioma, and hyperemesis gravidarum, decided to evaluate this observation by use of vaginal smears. Thirty-two cases of hyperemesis were compared to six nonpregnant cases and twenty normal pregnancies, each six months pregnant. He found that the squamous cells were predominantly acidophilic in the nonpregnant group. The cytology in the first trimester is the same as in the nonpregnant save for a slight increase in the number of basophilic staining cells. The cells in the last trimester of pregnancy take predominantly a basophilic stain. Those patients exhibiting hyperemesis gravidarum showed principally acidophilic staining reaction which agrees with the anticipated estrogenic deficiency and hyperprolanuria. CLAIR E. FOLSOME.

Sterility, Fertility, Contraceptives

Weinstein, B. Bernard: The Surgical Management of the Tubal Factor in Sterility, South. Surgeon, page 556, Aug., 1948.

Tubal occlusion is the largest single sterility factor in the female. Kymographic tracings obtained under carbon dioxide insufflation permit differentiation of diagnosis into: (a) normal patency, (b) nonpatency, (c) tubal spasm, (d) tubal stenosis. Salpingography

under Rayopake installation permits localization of the occluded point. An attempt to establish patency should be made by repeated injection of Lipiodol, diathermy, chemotherapy, and estrogen administration. These methods failing, surgery must be considered. The usual techniques for establishing tubal patency are reviewed, but preference is not expressed for any one of these. The author is experimenting with a sugar stick in cases of tubal resection with anastomosis. The importance of repeated insufflation following surgery is emphasized. WILLIAM BICKERS.

Popenoe, Paul: Infertility and the Stability of Marriage, West. J. Surg., page 309, May, 1948.

Infertility is the precursor to divorce. It is estimated that the childless marriages have divorce incidence of 70 per cent; whereas, in the group of couples with even one child, the incidence of divorce falls to 8 per cent. It must be remembered that half of all the childlessness is voluntary. Among 3,013 permanently childless marriages, farmers were found to have the lowest incidence of voluntary sterility (42 per cent), while the highest incidence was found in the professional groups (57 per cent).

Some of the partners involved in childless marriages are so inferior psychologically, physically, or socially that their childlessness may be socially or eugenically desirable. In the divorced population, which is largely made up of partners to previous childless marriages, the incidence of crime, insanity, and suicide is high. Life expectancy in the divorced population is about one-half that in the married group. It must be inferred that the divorced population is biologically inferior. Proper attention to sterility factors will aid those who are socially and eugenically sound, since they are the ones usually seeking aid. WILLIAM BICKERS.

Robertson, Jarratt P.: Semen Analysis in 204 Cases of Sterile Marriage, South. M. J. 41: 537, June, 1948.

About 10 per cent of all marriages in America are barren, and it is estimated that one-tenth of these sterile matings are the result of semen defects. Adequate examination of semen includes tests of volume, viscosity, number of spermatozoa per c.c., motility, survival time, and morphology. Taking the accepted standard of 3 c.c. volume, 60,000,000 sperm per c.c., 75 per cent motile after one hour, and a viability of twenty-four hours with abnormal forms not exceeding 25 per cent, sixty-two per cent of the 204 males studied were subfertile or sterile. Absolute sterility was present in 22 males, or 10 per cent of the total. Eight female partners in the subfertile group were sterile, leaving 98 possible conceptions for the entire group. Conception occurred in thirty, eighteen of whom delivered normal children. Since there is no satisfactory therapy for the subfertile male, with the possible exception of thyroid for those with a low basal metabolism rate, it must be assumed that the thirty conceptions are at least partially the result of medical treatment directed at raising the relative fertility of the female. WILLIAM BICKERS.

Correspondence

Mucocele of the Cervical Stump

To the Editor:

In the February, 1949, number of the JOURNAL (Vol. 57, No. 2, pages 341-344) I wrote an article on "Mucocele of the Cervical Stump." This article started with the sentence, "No reference to mucocele of the cervical stump could be found in the study of the literature." Purely by accident, I just came across an article entitled "Report of Case of a Large Mucocele of the Cervix, Following a Supravaginal Hysterectomy Fourteen Years Previously," which appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Vol. 9, page 349, 1928, written by Frederick A. Cleland of Toronto, Canada. In this article Dr. Cleland states, "I have been unable to find in the literature anything similar to this specimen, ... " His case is identical with the one that I encountered except that the external os was completely obliterated and that the nature of the tumor was therefore not recognized. In consequence of this, a difficult but successful operation was performed from above.

In justice to Dr. Cleland, his article should be mentioned.

ROBERT T. FRANK, M.D.

1035 PARK AVENUE
NEW YORK, N. Y.

Removal of the Umbilical Stump

To the Editor:

For some time it has been my routine to remove the umbilical stump as early as the fifth day after birth. The procedure consists of the simple maneuver of twisting the stump off either with the fingers and a piece of gauze cord dressing, or with a hemostat. The oozing base is touched with a silver nitrate applicator, and then covered with a tincture of Merthiolate dressing.

Although this routine has been followed in well over a thousand cases, not a single instance of hemorrhage or other untoward sequela has occurred in the entire series.

I have found the procedure a worth-while service. It eliminates the occasional odoriferous stump, and avoids the distasteful chore of repeated cord dressings sometimes lasting over a period of two or more weeks. It also admits of earlier immersion baths.

A thick stump occasionally delays the procedure two or three days.

The procedure is so simple and yet so practical that I hesitate to report it. However, I have never found it mentioned in any literature or textbook, and have never seen it performed in any clinic. I heartily recommend it.

C. O. MCCORMICK, M.D.

621 HUME MANSUR BUILDING
INDIANAPOLIS, IND.
SEPTEMBER 28, 1949

Pituitary Radiation for Sterility

To the Editor:

An evaluation of the results obtained in a comparatively large number of cases of sterility by the administration of estrogens and by pituitary irradiation is aptly presented in the September issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY by Dr. Rita Finkler. An impressive array of favorable reports by a number of investigators who employed the application of roentgen rays to the pituitary gland for this purpose is quoted, with emphasis on the therapeutic value of this procedure. It is obvious that the origin of this addition to the therapeutic armamentarium carries considerable interest. Credit for the introduction is given to Béclère, who "in 1926 reported the beneficial results of roentgen irradiation of the pituitary in a case of secondary amenorrhea."

Based on extensive experimentation, which revealed the reciprocal interrelations between the anterior hypophysis and the ovaries and stressed the relative immunity of the adult brain to x-rays, a series of cases of functional bleeding and of bleeding due to fibroids were subjected to pituitary irradiation. The remarkable therapeutic results obtained were reported in 1922 (*Archiv für Gynäkologie,* vol. 117). Subsequently, the indications were amplified. In 1923 our report covered the experiences with this method in a considerable number of cases of functional bleeding, uterine fibroids, cervical carcinoma as a preliminary to radium insertion, diffuse hyperplasia of the thyroid, and ovarian insufficiency (*Archiv für Gynäkologie,* vol. 120). Menopausal symptoms and sterility were later additions to the list of indications. The rationale of pituitary irradiation in cervical carcinoma as an effective means of inhibition of abnormal hypophyseal activity was fully discussed in a thesis published in the *Journal of Obstetrics and Gynaecology of the British Empire,* vol. 46, 1939. Thus, radiation of the hypophysis in cervical and mammary carcinoma tended to ascertain the same principle which in the present underlies the utilization of testosterone for these purposes. It is gratifying to find in the modern literature various reports which corroborate our findings of "pseudomalignant changes in the endocervix of the pregnant uterus," as first described in this JOURNAL, June, 1933, and clearly demonstrate that the endocervix represents the target organ of the adenohypophysis and, in turn, of the ovary. The possibility that irradiation of the pituitary in sterility may have a specific influence on the secretion of the endocervix must be borne in mind.

J. HOFBAUER, M.D.

GIBSON HOTEL
CINCINNATI, OHIO
OCTOBER 1, 1949

Reply by Dr. Finkler

To the Editor:

I have just received a letter from Dr. J. Hofbauer relative to my article entitled, "Evaluation of Hormonal and Radiation Therapy in 190 Cases of Functional Sterility and Secondary Amenorrhea" which appeared in the September, 1949, issue of the JOURNAL.

Unfortunately, I overlooked the matter of Dr. Hofbauer's priority in using radiation therapy to the pituitary gland and I will greatly appreciate it if you will be good enough to make this correction.

RITA S. FINKLER, M.D.

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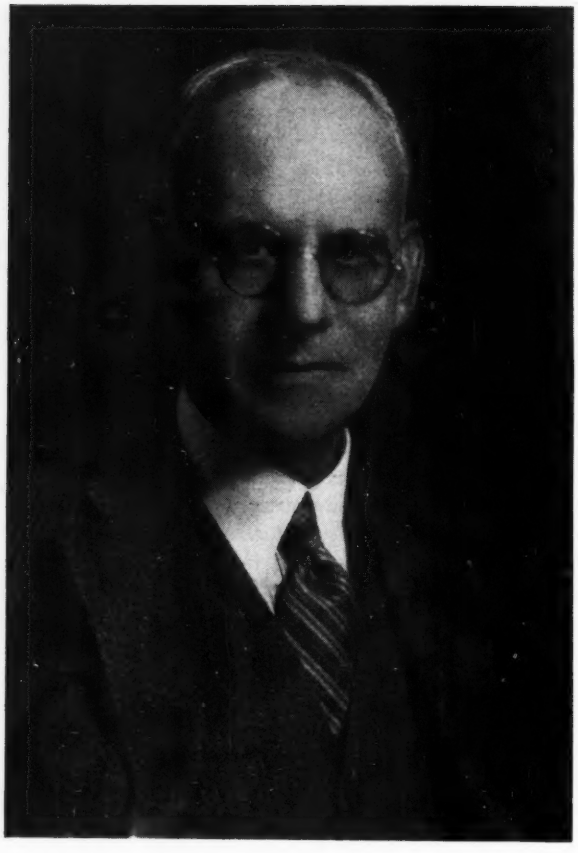
NEWARK, N. J.
OCTOBER 4, 1949



Robert Tilden Frank

1875—1949

Necrology

DR. ROBERT TILDEN FRANK, gynecologist, eminent endocrinologist, a member of the Publication Committee, of the Advisory Editorial Board of the JOURNAL since its founding, and likewise the Editor of the Department of Book Reviews, died in New York City on October fifteenth after a brief illness, at the age of 74.

A native of New York, Dr. Frank received his A.B. at Harvard in 1905 and his M.D. at the College of Physicians and Surgeons in 1909. In 1906 he began his long association with the Mount Sinai Hospital, became attending gynecologist in 1925, and continued in this capacity until he was made consultant in 1937. He likewise founded the Endocrine Research Laboratory at the institution in 1925 and remained as its head until 1944. He did pioneer work in this field and was the first to demonstrate the female sex hormone in the follicular fluid of the human ovary.

During the first world war Dr. Frank served in France with the A.E.F. as a captain and on his return to this country found it necessary, for reasons of health, to reside in Colorado, where he became associated with the University and General Hospitals as attending gynecologist and also continued his studies in endocrinology. He was the author of many outstanding contributions to the literature in this field.

Dr. Frank was a member of many specialist societies, including the American Gynecological and the New York Obstetrical, which he had served as President.

The Editor of the JOURNAL desires to add a personal note to the foregoing, for Robert Frank was closely associated with the early development of our publication and contributed much by his valuable advice and conscientious devotion to the work of his Department. The latter will be continued by Dr. Philip F. Williams of Philadelphia who was long associated with Dr. Frank in this capacity. The JOURNAL owes a tribute to the memory of Dr. Frank for his many years of active and helpful participation in its conduct.

Items

American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 3, 1950.

Arrangements will be made so far as is possible for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held May 21 to 28, inclusive, 1950, at the Shelburne, Atlantic City, N. J. Notice of the exact time and place of the Part I and Part II examinations will be sent all candidates well in advance of the examination date.

New Bulletins are now available for distribution upon application and give details of all changes in Board requirements and regulations made at the annual meeting of the Board held in Chicago, Ill., May 8 to 14, inclusive, 1949.

Application forms and Bulletins are sent upon request made to

PAUL TITUS, M.D., SECRETARY-TREASURER,
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY,
1015 HIGHLAND BUILDING,
PITTSBURGH 6, PA.

Increase in Size of the Journal

Our readers are notified that, beginning with the January issue, the JOURNAL will be enlarged to a total of 232 pages of reading matter. See announcement on page 36 of the advertising section of this number.